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VOLUME XXXVI • NUMBER 3
SEPTEMBER 1959

DISEASES of the CHEST

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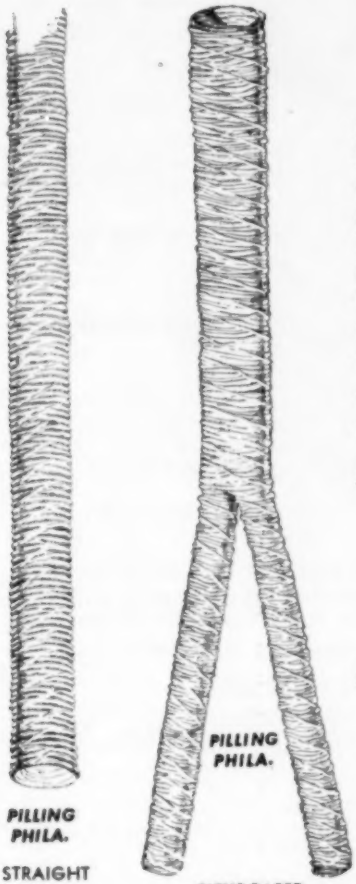

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1. DeBakey, M. E., Cooley, D. A., Morris, G. C., Jr., Collins, H.: Arteriovenous Fistula Involving the Abdominal Aorta, Annals of Surgery, 147:646 (May, 1958).

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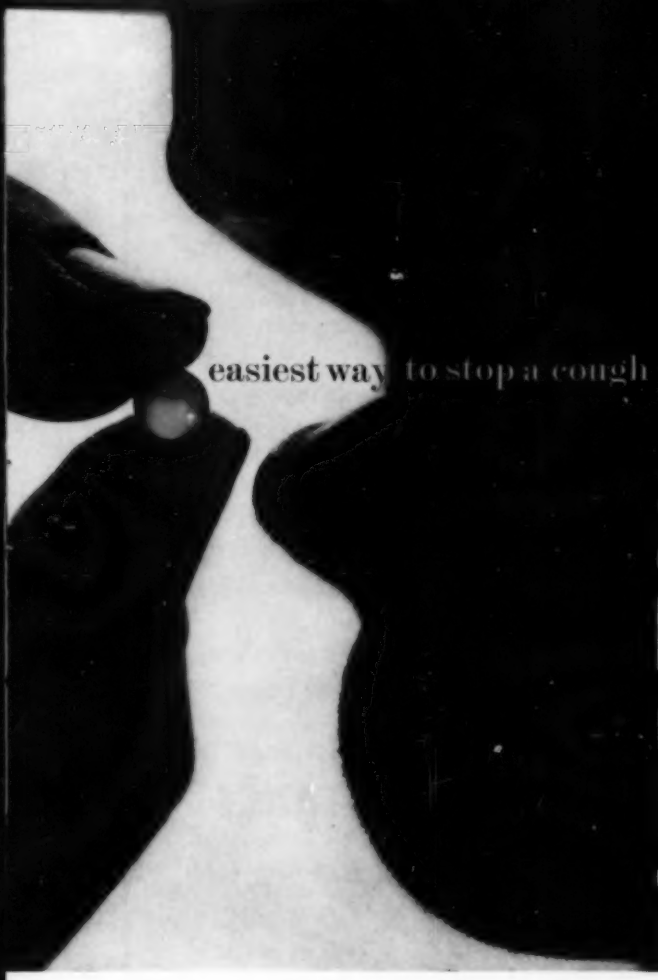

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1. Shane, S. J., Krzyski, T. E., and Copp, S. E.: Canad. M. A. J. 77:600 (Sept. 15) 1957.

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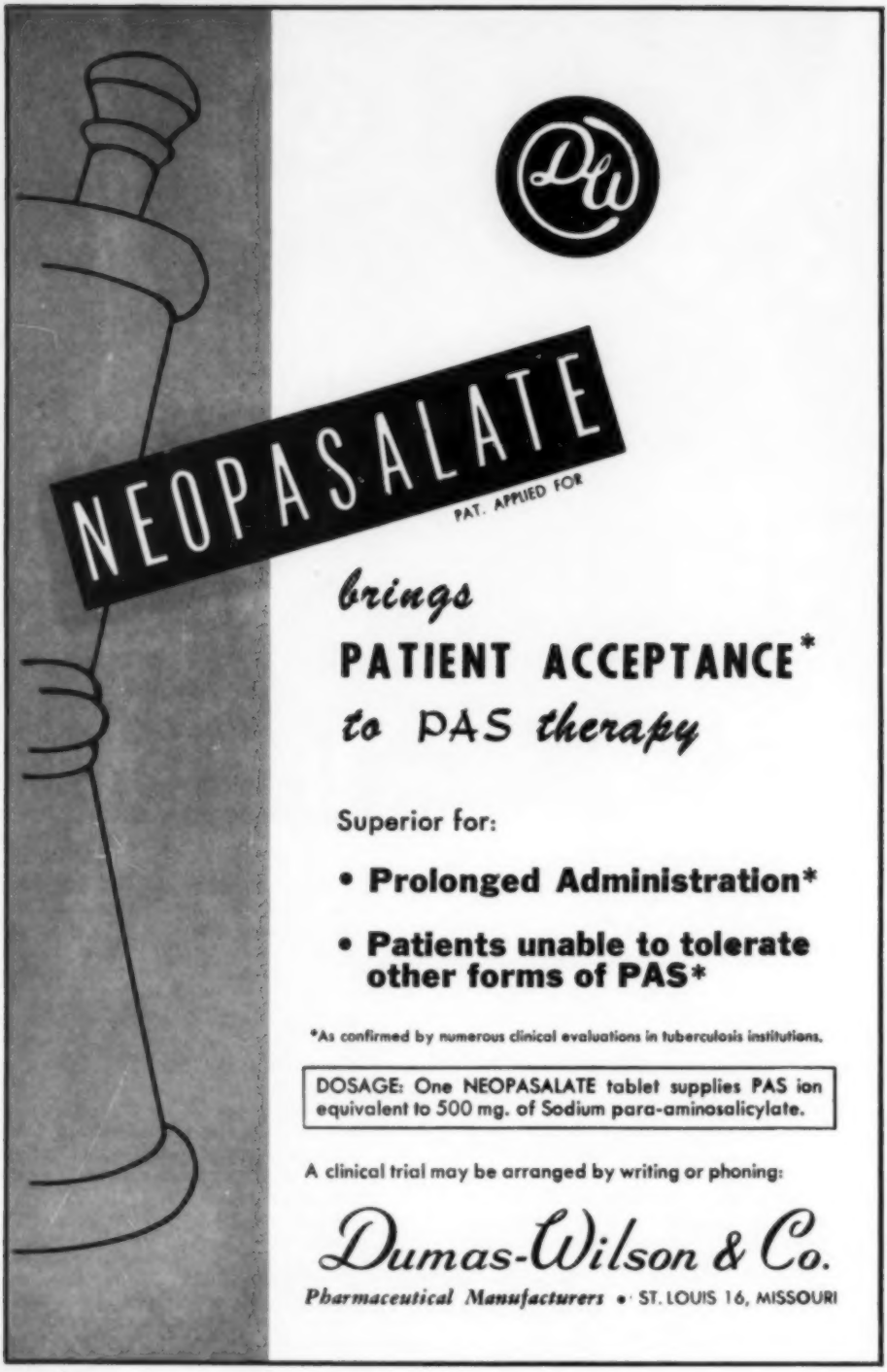
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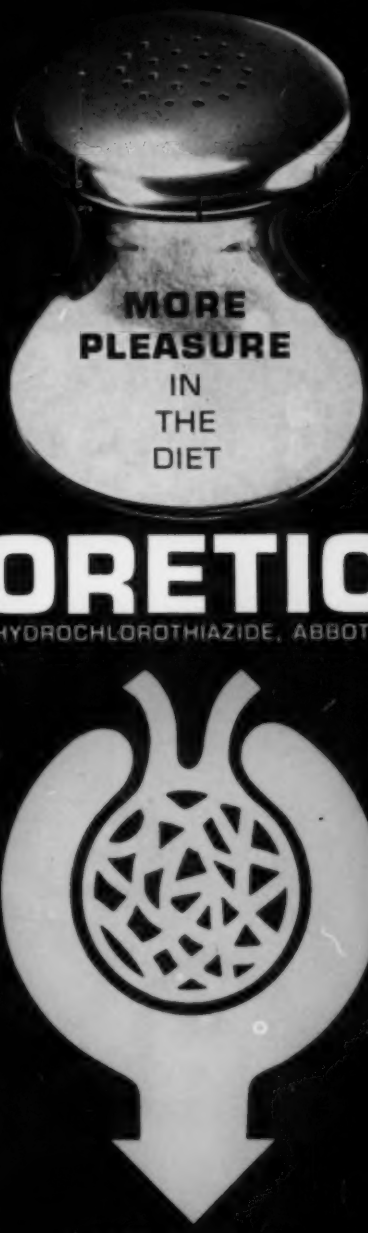

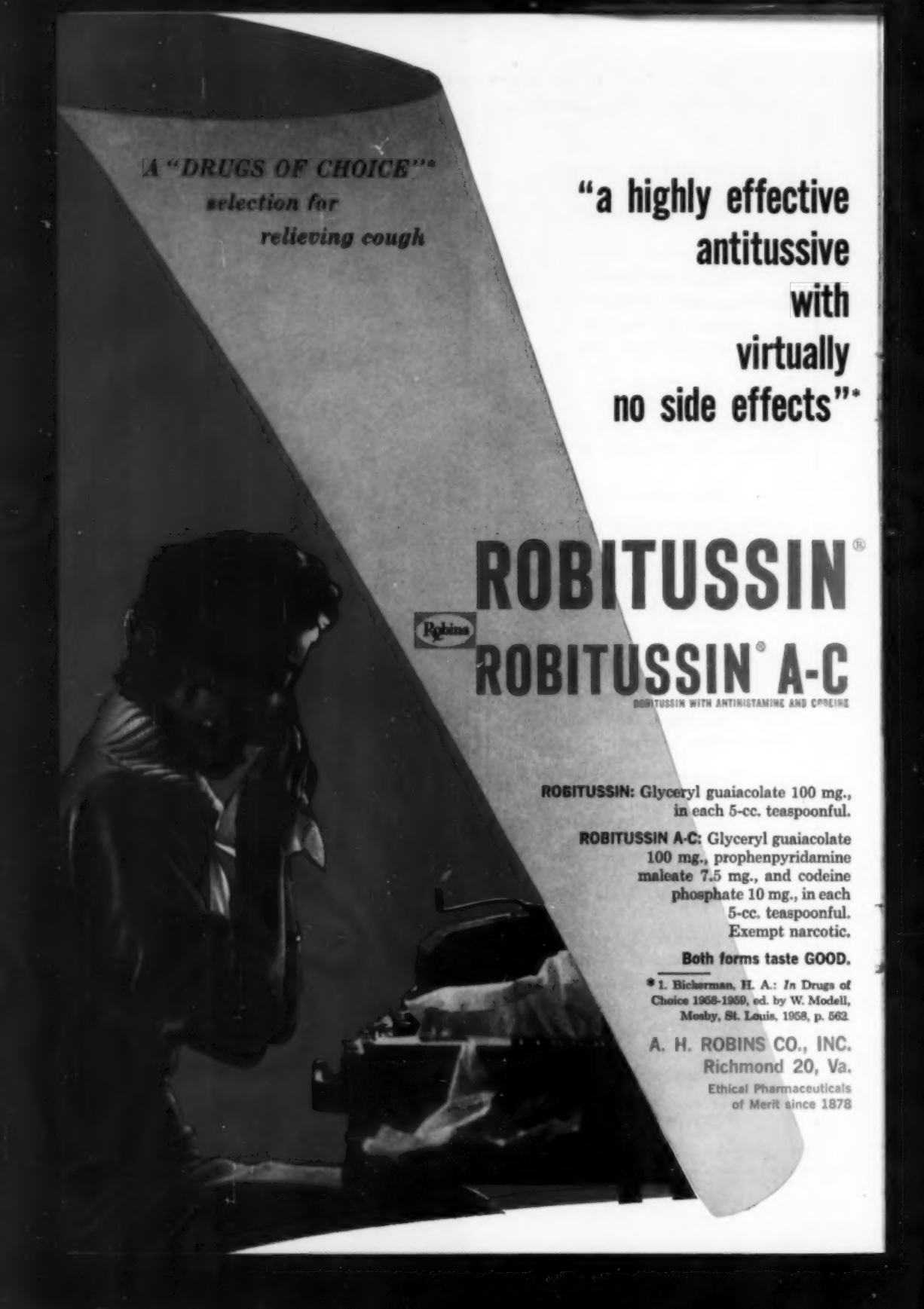
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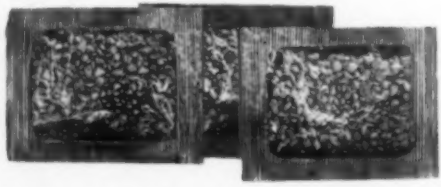

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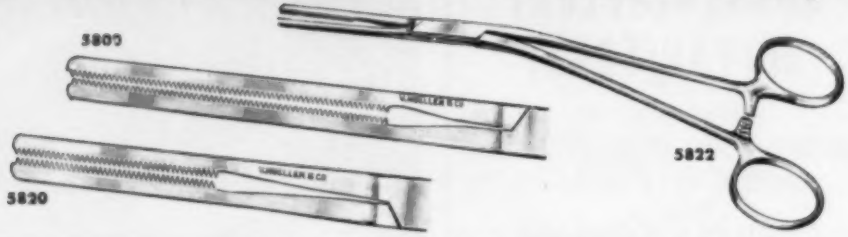

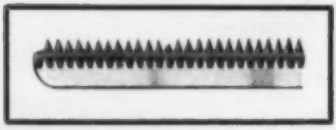

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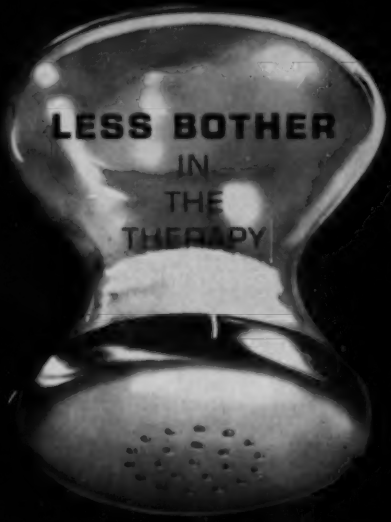

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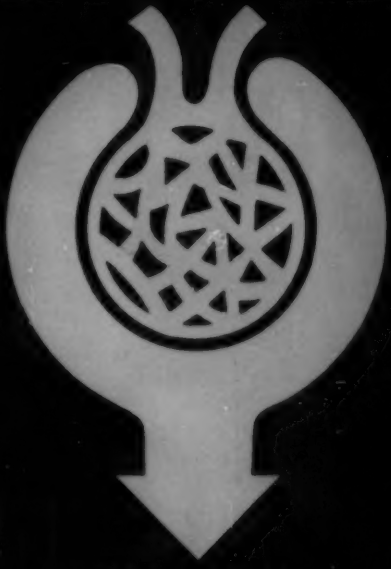

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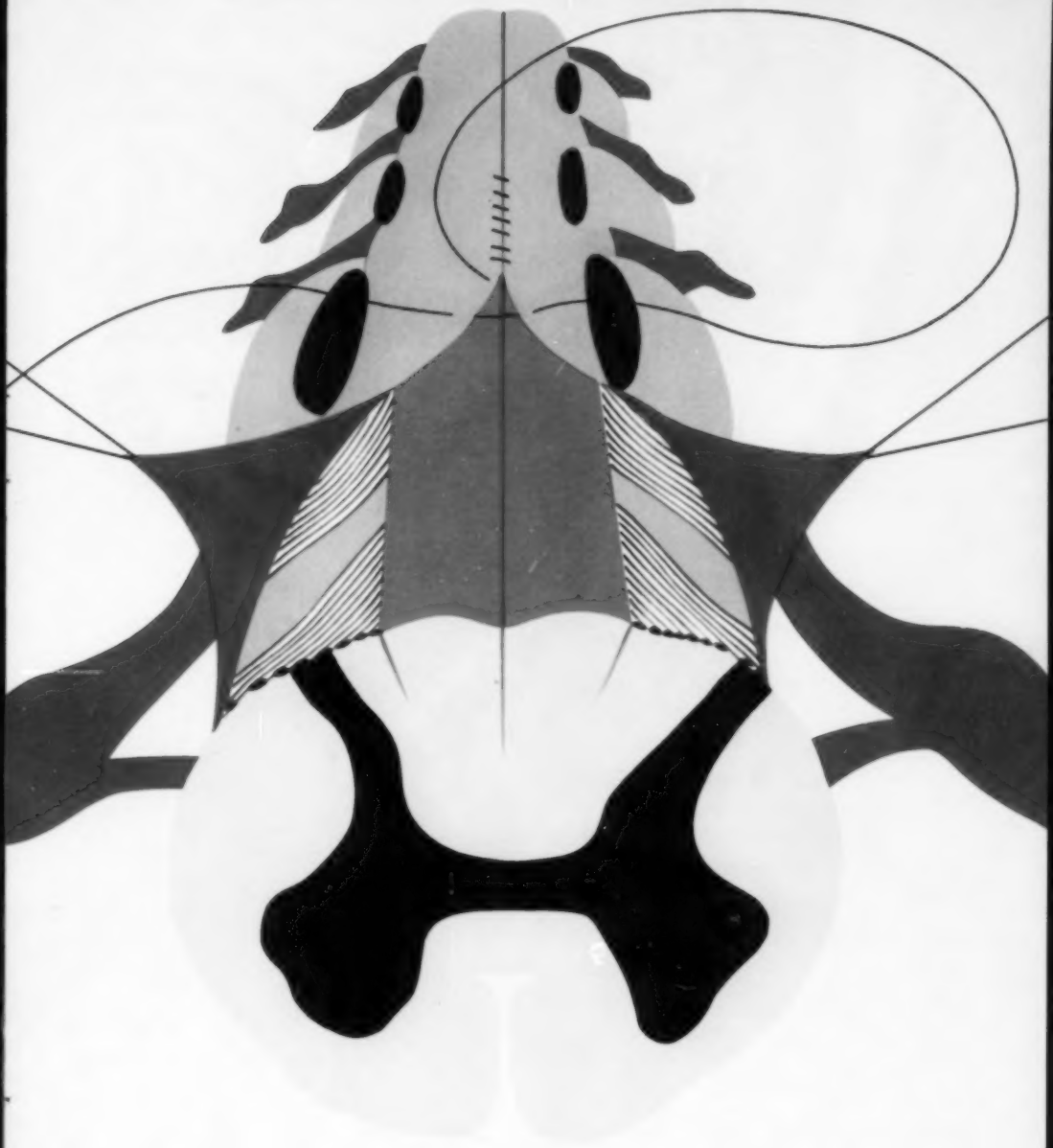

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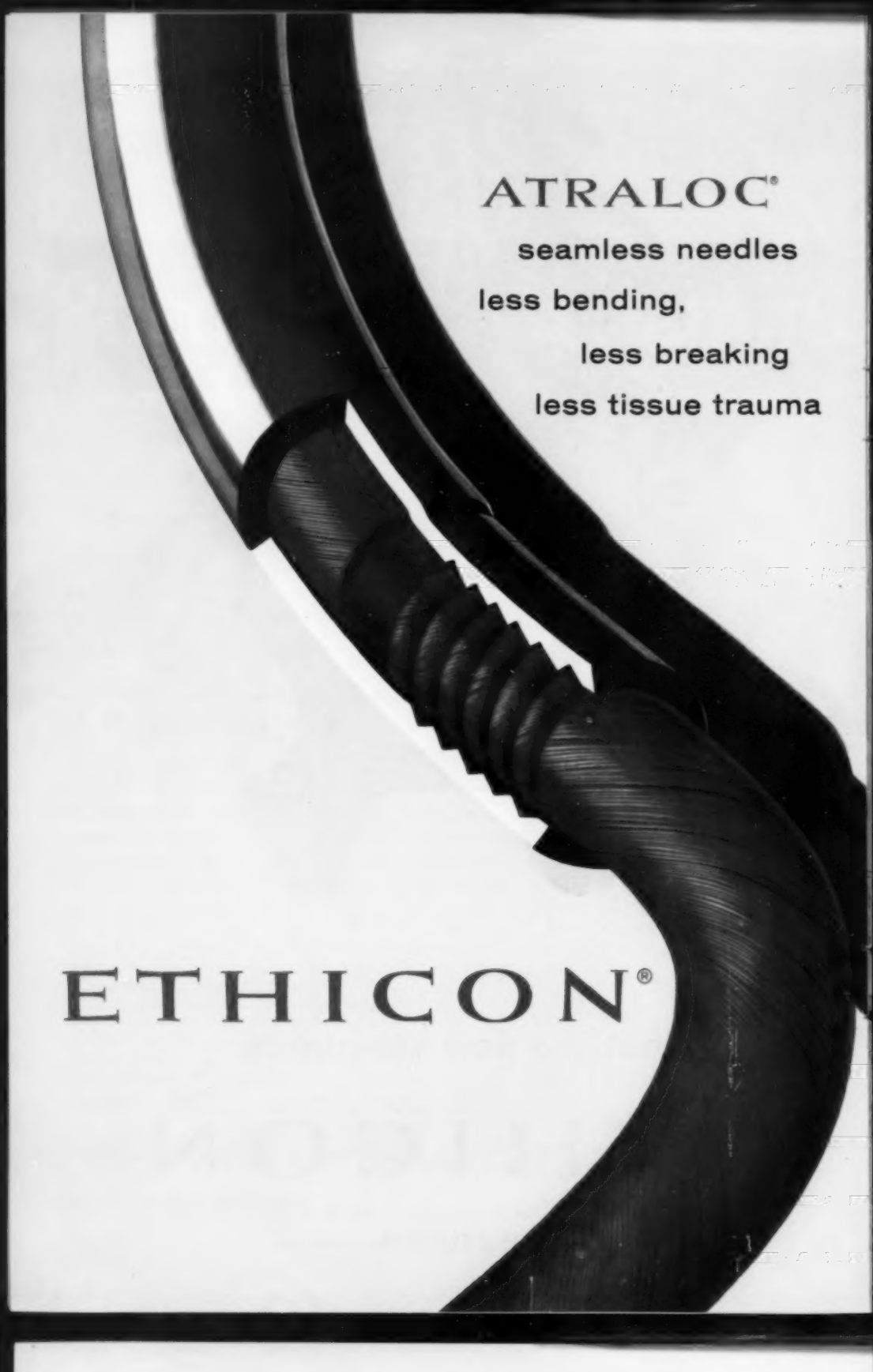
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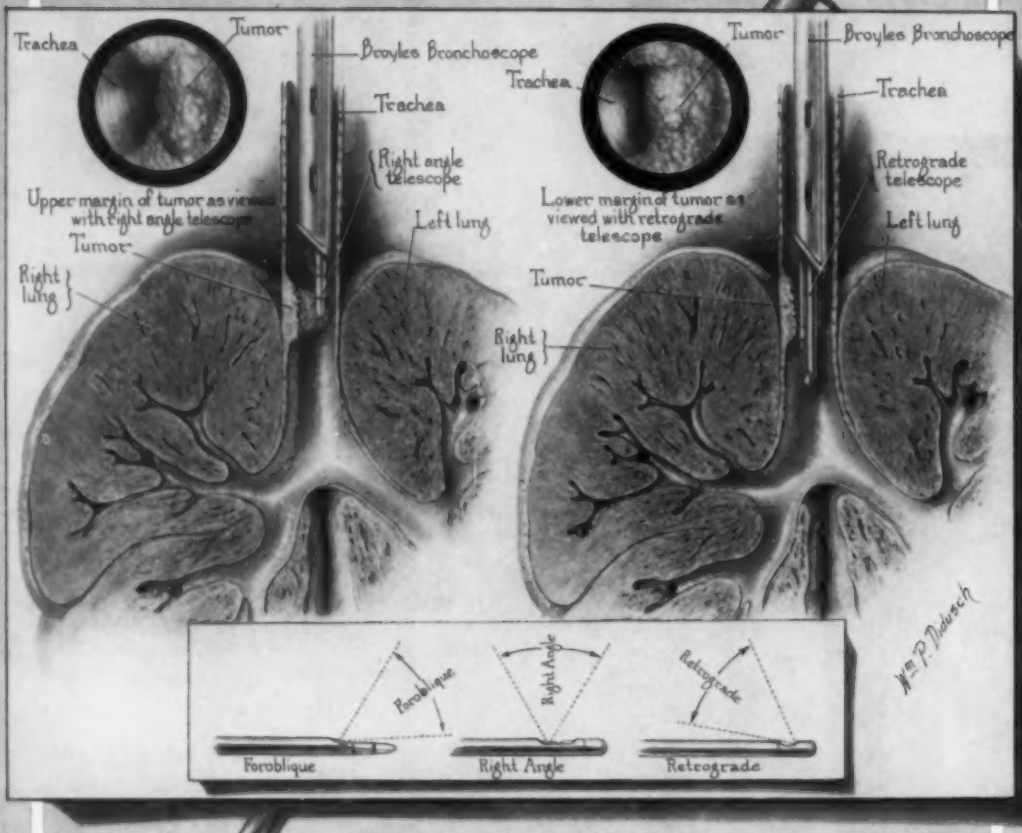

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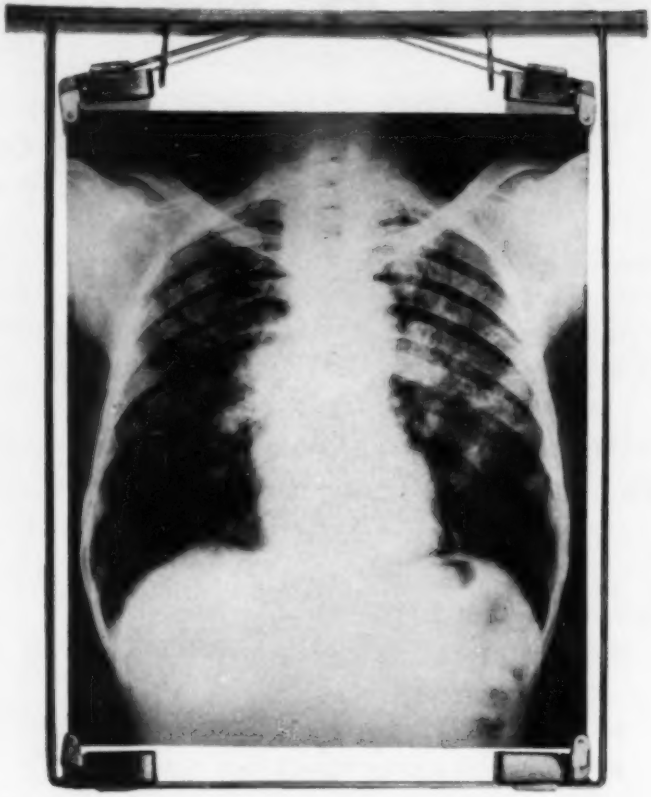

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References: 1. McLean, R. L., and Benson, W. R.: Tr. 15th Conference on Chemotherapy of Tuberculosis, 1956, p. 122. 2. Murdoch, J. M., and Stewart, S. M.: Brit. J. Tuberc. 50:85 (Jan.) 1956.

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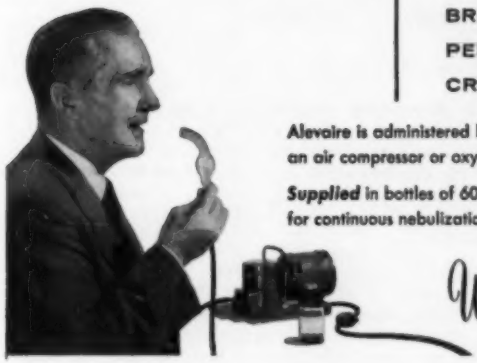

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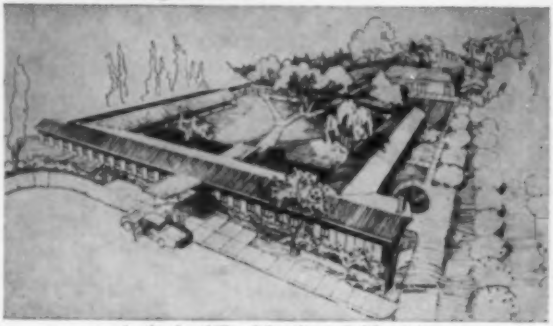

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. 234:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. 233:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. 3:229, Feb. 1959.

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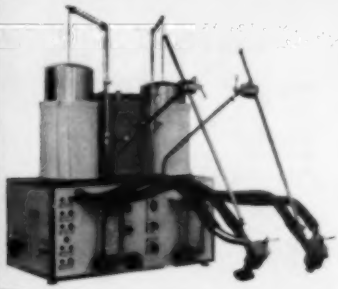

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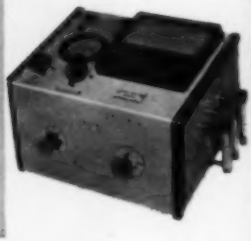

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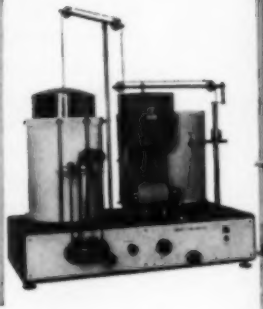

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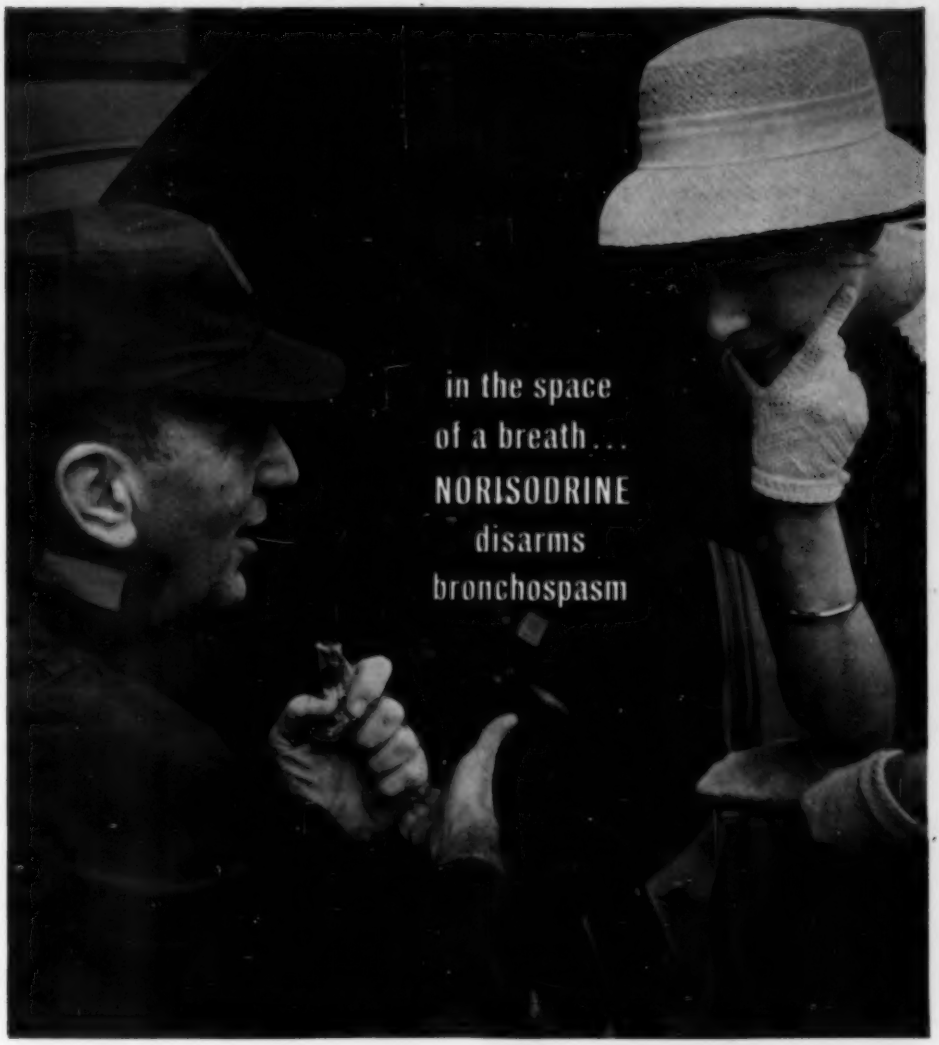

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CURRENT OXYGEN CONTROL METHODS UNSATISFACTORY

Control of oxygen concentrations in tents has always been difficult, requiring frequent analysis with an oxygen analyzer plus constant adjustment of the flow. Many factors can affect the concentration: Leaks in the tent, poor canopy tucking, inadequate liter flows, failure to use flushing procedures. Even the most elaborate inhalation therapy department cannot afford the necessary technicians to make certain proper oxygen concentrations are maintained.

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NEW ELECTRONIC UNIT ASSURES CONSTANT OXYGEN CONTROL

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The desired percentage of concentration is set on a meter – just like the desired temperature. The electronic control unit automatically adjusts the flow of oxygen to maintain the prescribed concentration. This new oxygen concentration control unit, called the O.E.M. AUTOMATIC MECHANAIRE, is perhaps the most important advance in oxygen tent therapy since the tent was invented.

HOW THE CONTROL UNIT WORKS

A sample of the atmosphere under the canopy is constantly being drawn into a continuous oxygen analyzer. Every 15 seconds, the concentration is monitored. The control unit maintains the concentration within a 6% range.

When the monitor finds the concentration below the range, oxygen at 40 liters a minute is flushed into the tent. There is a visual indication that oxygen is flushing into the tent. Oxygen continues to flush into the unit until the concentration is within the preset range. When the monitor discovers this, the flow of oxygen drops to a maintenance flow of 12 liters per minute . . . visually indicated on the control panel. If the oxygen concentration rises above the desired range, maintenance flow is cut off and air is flushed into the tent to bring the concentration down.

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Note that when a lower concentration is desired, it is not achieved merely by shutting off the oxygen flow. On the O.E.M. *AUTOMATIC* MECHANAIRE, an automatic air safety valve starts drawing room air into the tent as soon as the oxygen flow drops below 6 liters per minute. There is no danger of carbon-dioxide build-up because either air or oxygen in substantial quantities is being drawn into the canopy constantly, washing out the carbon-dioxide.

CLINICAL TESTING SHOWS ADVANTAGES

Under clinical conditions, the oxygen concentration in a new O.E.M. AUTOMATIC MECHANAIRE was brought up to 50% from room air in 10 minutes by electronic control. In comparison, more than an hour was required to bring a tent up to 50% concentration at the normal flow rate of 10-12 liters per minute.

The new O.E.M. AUTOMATIC MECHANAIRE maintained a 50% oxygen concentration for a 24-hour period under clinical conditions...on the maintenance flow of 12 liters per minute 96% of the time and on the flush cycle only 4% of the time. It maintained 60% oxygen concentration under clinical conditions on the maintenance flow of 12 liters of oxygen per minute for 90% of the time . . . and on flush for 10% of the time. Conclusive evidence that the new O.E.M. AUTOMATIC MECHANAIRE can maintain high concentrations of oxygen for therapeutic purposes with an economical consumption of oxygen.

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The O.E.M. AUTOMATIC MECHANAIRE including tent and electronic concentration control unit sells for $1,500. The control unit alone – which fits any model #50 or #55 Mechanaire – is $850. Control units for model #30 Mechanaires and tents not manufactured by O.E.M. are available on special order at slightly higher prices.

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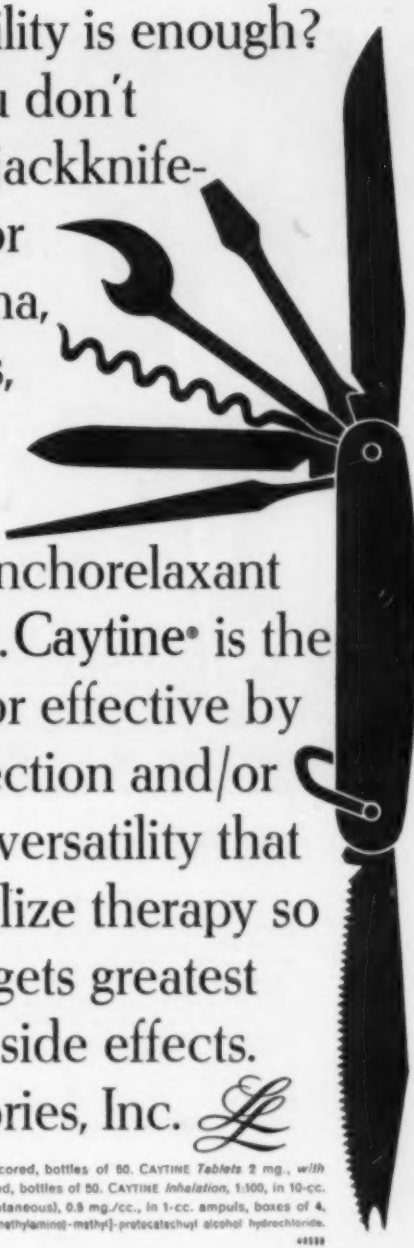

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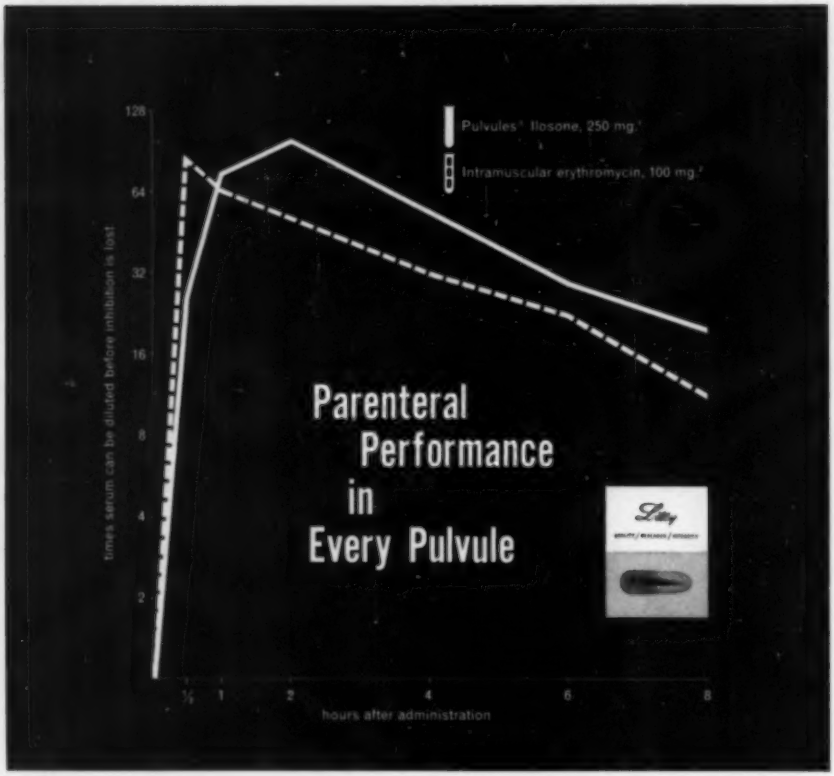

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1. Antibiotic Med. & Clin. Therapy, *5*:600, 1958.
2. Data from Antibiotics Annual, p. 289, 1954-1955.

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DISEASES of the CHEST

VOLUME XXXVI SEPTEMBER, 1959 NUMBER 3

The Solitary Circumscribed Pulmonary Lesion Due to Bronchogenic Carcinoma: a 3-year Follow-up Study of 94 Surgically Treated Patients

JOHN W. VANCE, M.D.,* C. ALLEN GOOD, M.D.,**
CORRIN H. HODGSON, M.D., F.C.C.P.,*** JOHN W. KIRKLIN, M.D.†
and ROBERT P. GAGE, M.S.‡

Rochester, Minnesota

Most reports of survival rates of patients treated surgically for bronchogenic carcinoma include lesions of varying roentgenographic appearance. The small pulmonary nodule has been singled out by some for special attention, and survival rates of 50, 62 and 75 per cent for a period of two years have been reported in such cases.[1-3]

A certain number of patients with bronchogenic carcinoma present roentgenographic evidence of a solitary circumscribed pulmonary lesion the first time they are examined. It was felt worth while to review the data on such patients who had undergone surgical treatment at the Mayo Clinic, to see whether these patients might differ from other patients with bronchogenic carcinoma, particularly as regards prognosis after surgical treatment.

Method of Study

Criteria used for the selection of cases were as follows: 1. The lesion had to be solitary, to be situated in the substance of the lung, to be more or less round, and to have a more or less well-defined border. 2. The lesion could not be associated with peripheral obstructive changes, central cavitation or pleural effusion. 3. The diagnosis of bronchogenic carcinoma must have been made on the basis of pathologic examination of the excised lesion.

For the 11-year period 1944 through 1954, a total of 94 cases met the foregoing criteria. Case records and roentgenograms of the thorax, when available, were studied. Follow-up of those patients who had not been examined at the clinic since January 1, 1958, was accomplished by letter. Many of the cases used in this study have been reported previously by either Hood and co-workers[4] or, more recently, by Good and Wilson.[5]

*Fellow in Medicine, Mayo Foundation.
**Section of Roentgenology.
***Section of Medicine.
†Section of Surgery.
‡Section of Biometry and Medical Statistics, Mayo Clinic and Mayo Foundation.
The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

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Material for Study

Seventy-six of the 94 patients were men. All but two were 40 years of age or older and 49 patients were 60 years old or older. The age and sex distribution is shown in Table I.

Fifty-two of the lesions were larger than 4.0 cm. in diameter, 21 were 3.1 to 4.0 cm., 16 were 2.1 to 3.0 cm., and only five were 2.0 cm. or less in diameter. No lesion measuring less than 1 cm. in diameter was treated by resection during the period of study. The lesions were found in the following distribution throughout the lung: right upper lobe, 30; right middle lobe, two; right lower lobe, 24; left upper lobe, 21; and left lower lobe, 17. Not one of these lesions showed evidence of calcification on roentgenographic examination of the thorax.

Results

Although on clinical grounds all patients were thought operable, nine of the 94 patients were found to be inoperable at the time of exploration, usually because of extensive mediastinal metastasis. The resectability rate, then, was 90 per cent. Operative procedures in the 94 patients were as follows: Exploratory thoracotomy, nine; pneumonectomy, 44 (two palliative); bilobectomy, eight (one palliative); and lobectomy, 33. Palliative operations were those in which it was apparent at operation that not all of the diseased tissue could be excised; there were 12 such procedures. This leaves 82 patients who had resection for what appeared to be all of the evident carcinoma, giving a "resection-for-cure" rate of 87 per cent.

Five of the 94 patients died in the hospital. Of these, two died of postoperative pulmonary insufficiency 2 days after pneumonectomy, in 1951 and 1953. The third patient, a 60-year-old man, died of acute pulmonary edema 2 days postoperatively after pneumonectomy in 1953 for a lesion 4.5 cm. in diameter in the right lower lobe. The fourth patient, a 62-year-old man, died of uremia 8 days after right upper lobectomy for a circumscribed pulmonary lesion 7 cm. in diameter. At necropsy, metastatic lesions in the brain and adrenal gland were demonstrated. The fifth hospital death was that of a 68-year-old, symptom-free man who died of

TABLE I—AGE AND SEX DISTRIBUTION OF 94 PATIENTS WITH BRONCHOGENIC CARCINOMA THAT PRESENTED AS A SOLITARY CIRCUMSCRIBED PULMONARY LESION

Age, Years	Total		Male		Female	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
30-39	2	2.1	1	1.3	1	5.6
40-49	15	16.0	12	15.8	3	16.7
50-59	28	29.8	22	29.0	6	33.3
60-69	44	46.8	38	50.0	6	33.3
70 +	5	5.3	3	3.9	2	11.1
TOTAL	94	100	76	100	18	100
Mean, years	58.7		58.9		57.8	
Youngest, years	36		38		36	
Oldest, years	72		72		71	

uncontrollable hemorrhage from the pulmonary artery during excision of a 3-cm. lesion discovered in the right upper lobe three weeks earlier by means of a survey film made by a mobile x-ray unit.

Large cell carcinoma, adenocarcinoma and squamous cell carcinoma each accounted for about 30 per cent of the 94 lesions (Table II). Seventy-seven of the 94 patients had cytologic examination of either sputum or bronchial washings. Thirty-one of these examinations (40 per cent) were positive for carcinoma cells. Sixty-seven of the 94 patients had bronchoscopic examination. In only seven of these examinations (10 per cent) was a positive tissue diagnosis made.

All but one of the patients were followed and were eligible for the calculation of three-year survival rates.[6] This one patient was last known to be living two years after pneumonectomy. The follow-up date was taken as January 1, 1958. All nine of the patients upon whom only an exploratory thoracotomy was performed are dead. Seven of these nine patients died during the first year following operation, one died during the second year and one died during the third year. All three of the patients upon whom palliative resection was performed died during the first year following operation. Among the 82 patients who underwent resection with view to cure there were five hospital deaths and these are excluded in the calculation of survival rates. Of the 77 patients eligible for a three-year follow-up, 76 were traced and 34 patients lived three or more years following operation. This is a three-year survival rate of 44.7 per cent. This value is quite in line with that reported by Kirklin and his co-workers.[7] It is of some interest to know the survival rate based on the total series, independent of the type of treatment received. The three-year survival rate was computed to be 36.6 per cent (34 of 93 traced patients).

Table III gives the three-year survival rates according to cell type. Because of the relatively small number of patients in each group the survival rates are not too well determined and the differences obtained between the adenocarcinoma and the large cell groups or between the squamous cell and large cell groups are not significant. The relationship of prognosis to presence of thoracic symptoms, size of lesion, increased erythrocyte sedimentation rate, positive results on cytologic examination of the sputum, type of operation performed and presence of nodal involvement at operation is shown in Table IV.

TABLE II—CELL TYPES FOUND IN 94 PATIENTS WITH BRONCHOGENIC CARCINOMA THAT PRESENTED AS A SOLITARY CIRCUMSCRIBED PULMONARY LESION

Cell Type	Patients	
	Number	Per Cent
Large cell	30	32
Adenocarcinoma	29	31
Squamous cell	25	27
Small cell	3	3
Unclassified	7	7
TOTAL	94	100

It was surprising to find that the absence of involvement of lymph nodes as revealed by microscopic examination of the excised specimen altered the prognosis very little in this series. This finding is contrary to that of others[8] and will be discussed later.

Patients who had no thoracic symptoms had a three-year survival rate (53.1 per cent) approximately 15 per cent higher than that of patients who had such symptoms (38.6 per cent). A similar observation has been made by others.[9-10] Fifty-nine of the 94 patients had symptoms; 17 of these complained of hemoptysis (four had lesions that were 4.0 cm. in diameter or less) and six complained of symptoms attributed to pulmonary osteoarthropathy; four of the six had bone symptoms as their only complaint. In 10 of the 35 patients who were asymptomatic the lesion was discovered by means of mobile-unit survey-type roentgenograms of the thorax.

The three-year survival rate was less by roughly 10 per cent in patients with either positive cytologic findings or an erythrocyte sedimentation rate greater than 30 mm. in one hour (Westergren method). The finding of similar three-year survival rates for lesions greater than 4 cm. in diameter and for lesions 4 cm. or less was somewhat surprising. In this regard, however, two of the 12 patients that could not have all of their carcinoma excised had lesions that were 2.0 and 2.5 cm. in diameter respectively.

Because of the small size of the series, the answer to questions arising from consideration of several concomitant variables will have to await further experience or the combination of series from several large centers.

Comment

Survival rates for patients operated upon for a solitary circumscribed lesion of the lung due to bronchogenic carcinoma are no higher than the survival rates for a composite group of patients in which all types of resectable bronchogenic carcinoma are represented. Of the 94 patients reported on here, 93 who were followed for a three-year period postoperatively have an over-all three-year survival rate of 36.6 per cent. If only operations in which all apparent carcinoma was removed are counted, 76 cases are available for three-year follow-up; the survival rate for this

TABLE III—PATIENTS WITH SOLITARY CIRCUMSCRIBED PULMONARY LESIONS DUE TO BRONCHOGENIC CARCINOMA—CURATIVE RESECTIONS: 3-YEAR SURVIVAL RATES ACCORDING TO CELL TYPE

Cell Type	Patients		Lived 3 or More Years After Operation	
	Total	Traced	Number	Per Cent*
Adenocarcinoma	26	26	13	50.0
Large cell	25	25	11	44.0
Squamous cell	19	18	9	50.0
Small cell	1	1	0	—
Unclassified	6	6	1	16.7
TOTAL	77	76	34	44.7

*Based on traced patients. Inquiry as of January 1, 1958. Hospital deaths are excluded in the calculation of survival rates.

group is 44.7 per cent. This is almost the same figure as Kirklin and co-workers[7] obtained following curative resection for bronchogenic carcinoma regardless of the roentgenographic appearance of the lesion (151 cases from this institution). Gifford and Waddington[11] reported a survival rate of 39 per cent for the same period.

The resectability rate for the solitary circumscribed pulmonary lesion due to bronchogenic carcinoma in this series (90 per cent) is much higher than in the series of Kirklin and co-workers (49.8 per cent), and the operative mortality rate is considerably lower (5.3 per cent as compared with 13.6 per cent). The higher resectability rate for bronchogenic carcinoma presenting as a pulmonary nodule increases the over-all survival rate for patients with this form of bronchogenic carcinoma as compared with patients who have other forms of bronchogenic carcinoma.

TABLE IV

PATIENTS WITH SOLITARY CIRCUMSCRIBED PULMONARY LESIONS DUE TO BRONCHOGENIC CARCINOMA—CURATIVE RESECTIONS: 3-YEAR SURVIVAL RATES ACCORDING TO DIFFERENT VARIABLES

Variable	Patients		Lived 3 or More Years After Operation	
	Total	Traced	Number	Per Cent*
Thoracic symptoms				
Present	45	44	17	38.6
Absent	32	32	17	53.1
Total	77	76	34	44.7
Size of lesion				
4.0 cm. or less	43	43	19	44.2
More than 4.0 cm.	34	33	15	45.5
Total	77	76	34	44.7
Sedimentation rate (mm. in 1 hour)				
30 or less	39	39	20	51.3
More than 30	25	24	10	41.7
Unknown	13	13	4	30.8
Total	77	76	34	44.7
Cytologic findings				
Positive	20	19	8	42.1
Negative	44	44	23	52.3
Unknown	13	13	3	23.1
Total	77	76	34	44.7
Operation				
Pneumonectomy	41	40	17	42.5
Lobectomy	36	36	17	47.2
Total	77	76	34	44.7
Nodal involvement				
Present	34	34	14	41.2
Absent	40	39	19	48.7
Unknown	3	3	1	33.3
Total	77	76	34	44.7

*Based on traced patients. Inquiry as of January 1, 1958. Hospital deaths are excluded in the calculation of survival rates.

There was no significant difference in the survival rate for our patients whether pneumonectomy or lobectomy was the operation performed. It is noteworthy that the three-year survival rate for asymptomatic patients was about 15 per cent higher than that for patients with thoracic symptoms. Criteria for determination of the age of a lesion due to bronchogenic carcinoma are not well defined, but it seems reasonable to suppose that a group of solitary circumscribed pulmonary lesions associated with symptoms would, on the whole, be further advanced or "older" than a similar group not associated with symptoms. Efforts to uncover the asymptomatic lesion must continue in order to improve the survival of patients with bronchogenic carcinoma. In this series, 28.6 per cent of patients with asymptomatic lesions were discovered by mobile-unit survey-type roentgenograms of the thorax.

Early diagnosis and early surgical resection offer the greatest hope for improvement of survival rates in the present state of knowledge. It is sobering, however, to recall that the most favorable lesions were associated with a survival rate of about 50 per cent.

This and the fact that the survival rate in this series appeared about the same whether or not regional and hilar lymph nodes were involved with carcinoma can almost reasonably be explained by the proposition that distant spread of solitary circumscribed lesions of bronchogenic carcinoma occurs more by vascular pathways than by the lymphatic system. Ballantyne and co-workers[12] have recently demonstrated that vascular involvement had occurred in almost 100 per cent of surgical specimens of bronchogenic carcinoma examined at this clinic.

SUMMARY

For 94 surgically treated patients who had bronchogenic carcinoma that presented in the thoracic roentgenogram as a solitary circumscribed pulmonary lesion, the resectability rate was 90 per cent and the hospital mortality rate was 5.3 per cent. Cytologic examination of the sputum appeared to be of definite value in the preoperative diagnosis of the uncalcified solitary pulmonary lesion. The presence or absence of thoracic symptoms seemed to be the most significant prognostic variable studied.

The over-all three-year survival rate based on 93 traced patients was 36.6 per cent. The 3-year survival rate for patients who had excision of all apparent bronchogenic carcinoma was 44.7 per cent. Compared with a previous series reported from this institution, there was no essential difference in the three-year survival rates for resectable bronchogenic carcinoma whether or not it presented on the thoracic roentgenogram as a solitary circumscribed pulmonary lesion.

Present surgical treatment of bronchogenic carcinoma must be vigorously pursued with a maximal effort directed at early diagnosis and early surgical resection.

RESUMEN

Para 94 enfermos tratados quirúrgicamente con motivo de carcinoma bronquiogénico que se presentaron radiológicamente como lesión pulmonar circunscrita la resectabilidad fué de 90 por ciento y la mortalidad hospitalaria de 5.3 por ciento. El examen citológico del esputo pareció ser de valor definido en el diagnóstico preoperatorio de la lesión solitaria no calcificada en el pulmón.

La presencia o ausencia de síntomas torácicos pareció ser el dato variable de mayor importancia para el pronóstico.

La sobrevida general basada en 93 enfermos seguidos, fué de 36.6 por ciento a los tres años. La sobrevida a los tres años ampara los enfermos que tuvieron excisión completa de todo lo aparente del carcinoma bronquiogénico fué de 44.7.

Comparada con las series anteriores publicadas por esta institución no hubo diferencia esencial en la sobrevida a los 3 años del carcinoma bronquiogénico ya se presente o no en las radiografías como lesión pulmonar aislada solitaria.

El tratamiento actual del carcinoma bronquiogénico debe ser vigorosamente impulsado con un máximo de esfuerzo hacia el descubrimiento temprano y la temprana resección quirúrgica.

RESUME

Sur 94 malades traités chirurgicalement, alors qu'ils étaient atteints d'un cancer bronchique qui se présentait sur la radiographie thoracique comme une lésion pulmonaire isolée circonscrite, le taux opératoire fut de 90% et le taux de mortalité hospitalière de 5,3%. L'examen cytologique de l'expectoration apparut avoir une valeur précise dans le diagnostic préopératoire de la lésion pulmonaire isolée et non-calcifiée. La présence ou l'absence de symptômes thoraciques sembla être la variante la plus significative pour établir le pronostic.

Le taux moyen de 3 ans de survie, basé sur l'étude des 93 malades cités fut de 36,6%. Le taux de 3 ans de survie pour les malades qui avaient subi l'exérèse de tout cancer bronchique apparent fut de 44,7%. En comparaison avec une série antérieure rapportée devant cette société, il n'y eut aucune différence essentielle pour les taux de survie de 3 ans pour le cancer bronchique opérable, qu'il se soit présenté ou non sur la radiographie thoracique comme une lésion pulmonaire isolée et circonscrite.

Le traitement chirurgical actuel du cancer bronchique doit être vigoureusement poursuivi avec l'effort principal dirigé sur la possibilité d'un diagnostic et d'une résection chirurgicale précoces.

ZUSAMMENFASSUNG

Bei 94 chirurgisch behandelnden Kranken mit Bronchuscarzinom, das sich auf dem Lungenröntgenbild als ein umschriebener solidärer Herd darstellt, lag die Ziffer für die Möglichkeit der Resektion bei 90 Prozent und betrug die Anstaltssterblichkeit 5,3%. Die cytologische Untersuchung des Sputums schien definitiv von Wert zu sein für die präoperative Diagnose nicht verkalkter solidärer pulmonaler Herde. Das Vorliegen oder Fehlen thorakaler Symptome schien die bedeutsamste prognostische veränderliche Grösse bei der Analyse zu sein.

Die totale dreijährige Überlebensrate bei 93 nachbeobachtenden Kranken belief sich auf 36,6%. Die dreijährige Überlebensrate bei Kranken mit Exzision von allem augenfälligen bronchogenem Krebsgewebe betrug 44,7%. Im Vergleich mit früher mitgeteilten Patientenreihen aus unserer Abteilung bestand keine wesentliche Differenz für die dreijährige Überlebensziffer bei resektionsfähigem Bronchuscarzinom, unbeschadet dessen, ob sie auf dem Lungenröntgenbild als umschriebener solidärer Herd erschienen oder nicht.

Die heutige chirurgische Behandlung des Lungenkrebses muss mit allem Nachdruck weiter verfolgt werden mit maximalem Bemühen hinsichtlich der Frühdiagnose und frühzeitiger chirurgischer Resektion.

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Diabetes and Tuberculosis*

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This paper is based on observations of 200 patients who were afflicted with diabetes mellitus and complicating active pulmonary tuberculosis. Its presentation is prompted by the generally recognized increasing incidence of diabetes mellitus and by the high frequency of pulmonary tuberculosis in this condition. I critically reviewed the problem of the combined manifestations of these two diseases in previous reports which were published in the *American Review of Tuberculosis*, the *Archives of Internal Medicine* and in *Diseases of the Chest* in 1931 and 1944. Since then an additional number of patients of this category have been under my care. Also, during the intervening period pertinent issues have been clarified. Moreover, opportunity offered itself for the analysis of data based on modern antimicrobial therapy.

The prevailing multiplicity of concepts which deal with the causal connection between diabetes and tuberculosis attests to the uncertainty in this respect. The dominant manifestation of diabetes mellitus, namely hyperglycemia has been assumed to favor the growth, viability and propagation of tubercle bacilli. Furthermore, it was thought that the concomitant increase in dextrose in the tissues resulted in lessened resistance to infection *in situ* and also, in impaired repair capacity. Predilection to infection was attributed to local tissue acidosis with its imbalance of electrolytes. A number of investigators advanced the view that there was a lowering of protective cytological and immunological function which, in turn, brings about increased susceptibility to infection. Too, increased availability of glycerol and nitrogenous substances which aid the growth of tubercle bacilli, were considered possible contributory causes. In contemporary medical thinking the assumption is gaining ground that dysfunction of the pituitary gland may have a great deal to do with increased susceptibility to tuberculosis. A relative and absolute overproduction of adrenocorticotropic hormone and consequent increased supply of corticosteroids to the blood may interfere with the normal defense mechanism of mesenchymal tissues. As the result, exudative inflammatory response is enhanced, while formation of granulation tissue is retarded. Corticosteroids are insulin antagonists. Their overproduction may result in insulin-resistant diabetes.

Prevalence of pulmonary tuberculosis in patients with diabetes mellitus in contrast to the relative infrequency of extrapulmonary forms of tuberculosis in these patients seem to support my precept that hepatic dysfunction with its consequent hypovitaminosis A, plays a major causative role in this respect.

The clinical material which I assayed corroborates some of the reports of others as well as my previous findings. In addition, I wish to record further observations of interest. 1. The longer the duration of diabetes

*Presented at the 5th International Congress on Diseases of the Chest, Tokyo, Japan, September 7-11, 1958.

the greater is the likelihood of complicating tuberculosis. 2. Regardless of the severity of diabetes, patients whose disease is poorly controlled are more prone to develop tuberculosis than individuals with well controlled diabetes. 3. There is a high incidence of exudative type of involvement of the lung. 4. Tuberculous changes in the bronchial mucosa and in the bronchial wall are rare. 5. Bronchospasm is uncommon. 6. Tuberculous pleurisy with effusion is infrequent. 7. Extrapulmonary complications (osseous, meningeal and other forms) are conspicuously absent.

Some of these items should be commentated. The high incidence of exudative pulmonary lesions may be attributable to factors, such as hyperfunction of the pituitary gland, with consequent overproduction of adrenocorticotropic hormone, lowered bacteriostatic capacity of the blood, deficient tissue repair in the lung and possible interference with vitamin A metabolism by hypercholesterolemia.

Basal tuberculosis of the lung is not typical of diabetes mellitus. I have observed this type of lesion not infrequently in older, obese persons. Its occurrence may be attributable to mechanical interference with normal ventilatory function in this region of the lung which is brought about by excessive adiposity of the anterior abdominal wall and abdominal contents. In reference to exudative lesions, mention should be made of cavity formation in a rather high percentage of these cases. Atrophy of the bronchial mucosa may be only one of the manifestations of degenerative changes associated with hypovitaminosis A which render the lung an organ of lessened resistance in comparison to other parts of the body.

Data recorded in this study enable me to question the validity of some of the ideas advanced by others. It is not true that the onset of pulmonary tuberculosis is more acute in patients with diabetes mellitus than without diabetes. Roentgenologic character of pulmonary tuberculosis in patients with diabetes is not pathognomonic. Identical type of findings may be seen in tuberculous patients who have no diabetes. Tuberculous lymphangitis with "butterfly-type" perihilar changes is not of common occurrence. Three per cent of the group of patients I surveyed were twenty years of age or younger. This finding is contrary to the view that tuberculosis is frequent among juvenile diabetics.

Pointers on Diagnosis

Subjective symptoms may be trivial or transient. This phenomenon may be explained possibly on the basis of hyperfunction of the pituitary gland. Consequent overproduction of corticosteroids may counteract allergic reactions resulting from infection with tubercle bacilli. Fibrosis and narrowing of the lymphatics of the lung in senescent persons retards the passage of toxins and inflammatory products through these channels and thus likely to lessen toxic symptoms.

Bronchoscopic examinations in my patients revealed very low incidence of tuberculous involvement of the bronchi. I am of the opinion that hyperglycemia, through its osmotic influence, is likely to reduce the formation and accumulation of inflammatory exudate in these structures. In the absence of bronchial tuberculosis and in view of lessened exudate formation, one should anticipate less bronchospasm. Of course, increased blood level of corticosteroids acts as a potent bronchospasmolytic factor. Perhaps,

it is permissible to interpolate here that the surprisingly low incidence of allergic bronchial asthma in patients with diabetes mellitus is explainable on the basis of hypotheses offered in this paragraph.

It is reasonable to assume that paucity of symptoms constitutes a major reason for finding so few patients with minimal tuberculosis and so many with far advanced tuberculosis in the group I am presenting. Only 3.5 per cent belonged in the former category while 75 per cent in the latter.

Pointers on Prognosis

Uncontrolled diabetes mellitus or lapse in its control may cause flare-up or spread of tuberculosis.

In well-controlled diabetes the course of pulmonary tuberculosis is not different from that in patients without diabetes. In other words, as far as tuberculosis is concerned, the survival rate and socio-economic rehabilitation of adequately treated patients with diabetes and pulmonary tuberculosis are the same as that of tuberculous patients without diabetes.

Pointers on Treatment

Conversion from a status of positive for tubercle bacilli to negative can be accomplished in most instances by medical means, mainly by chemotherapy, antibiotics and by conservative relaxation therapy to the lung.

In very severe cases of pulmonary tuberculosis (miliary or extensive exudative lesion with large cavities) the combined use of streptomycin, isoniazid and para-aminosalicylates proved to be of value. In others good results were observed from the combined administration of streptomycin and para-aminosalicylates, isoniazid and para-aminosalicylates or from isoniazid alone. The latter was given in doses of 4 to 8 mg. per Kg. of body weight. Because of its possible hepatotoxic action, pyrazinamide should be used in exceptional cases only. Frequent liver function tests are required in such instances. As to para-aminosalicylates, sometimes changing to a different chemical form of this compound may obviate gastrointestinal disturbances.

Whenever elective surgical intervention is proposed, one should keep in mind the inevitable risk. Patients with diabetes undergoing major surgery are in need of meticulous care in their metabolic management. Their dextrose tolerance is lowered temporarily. So as to avoid slow wound healing, undue loss of body proteins and ketosis, it is mandatory to maintain the blood sugar below 200 mg. per cent. "Alarm reaction" in connection with surgery leads to increased outpouring of corticosteroids from the suprarenal glands into the blood stream. After operation, regular insulin is used in addition to longer lasting insulin for a few days while the patient is given 70 Gm. dextrose every six hours. Blood sugar is checked daily.

One should plan on rapid physical rehabilitation, in terms of months rather than years as it was practiced years ago. Therapeutic results in reference to tuberculosis were summarized in my report of 1944 as follows: Apparently arrested, 6.9, quiescent, 5.2, improved, 8.7, unimproved, 20.9 and died, 58.2 per cent. Since the era of modern antimicrobial therapy, the results were: Inactive, 10.7, discharged from the sanatorium for ambulatory home treatment with the classification of stage of activity undeter-

mined, bacteriologically negative, 54.7, improved, 12.0, unimproved, 6.6 and died 16 per cent. The contrast between the two groups is convincing and gratifying. In my experience, discharging patients of this category for home treatment has been highly successful. They are given periodic check-up examinations at the Outpatient Service of the sanatorium. Only 7.1 per cent of this group suffered a relapse which required their readmission to the institution.

In the management of diabetes I have found the following precepts serviceable. 1. Maintenance of blood sugar at normal or near normal level. It is permissible to carry the patient with blood sugar from 120 to 150 mg. per cent, with slight trace of urinary sugar. In female patients with labile metabolic balance, close watch is necessary during the menstrual period because of the higher insulin requirement at this time. 2. Avoidance of hypoglycemic reactions. It is well to keep in mind that toxic tuberculous patients with diabetes who are taking insulin are prone to hypoglycemic reactions, except the ones who are emaciated. 3. The patient should be kept free from acidosis and coma. Ketosis should be treated promptly and expeditiously. 4. Body weight is to be kept normal or slightly below normal. 5. Provisions should be made for a varied, attractive diet. One should remember that dietary indiscretions are common in this group.

Diabetes was controlled by tolbutamide (Orinase), a sulfonylurea, in some of my patients over 40 years of age. It was given orally in the form of tablets of 0.5 Gm. in accordance with the recommendation of the American Diabetes Association, namely, the first day, 3.0 Gm., second day, 2.0 Gm., third day, 1.0 Gm. The maintenance dose varied from 0.5 to 1.0 Gm. a day. No hepatotoxic effect or other complications were noted.

For years I have been advocating the administration of vitamin A as a replacement therapy. As a rule 25,000 units are given orally three times a day. This medication can be maintained for several years. I have never seen a case of vitamin A intoxication in my patients kept on this schedule for prolonged periods. The rationale of vitamin A medication was discussed in detail in one of my previous papers.

It is sound practice to abstain from the administration of corticosteroids. They render the diabetic metabolic balance unstable and thus necessitate the use of much more insulin.

SUMMARY

Material presented in this paper has been gathered from the author's experience with 200 patients who were afflicted with diabetes mellitus and complicating pulmonary tuberculosis. Concepts are reviewed which deal with the cause of increased susceptibility to tuberculosis of patients suffering from diabetes mellitus. Some peculiarities of the clinical substrate of pulmonary tuberculosis in these individuals are discussed. Therapeutic precepts applied in the treatment of the two diseases are outlined. In well controlled diabetes, adequate antimicrobials and adjunct measures are bound to bring about a recovery rate from pulmonary tuberculosis which compares favorably with that of tuberculous patients without diabetes. I have found that after proper institutional treatment, diabetics with pulmonary tuberculosis may become eligible for outpatient care, provided facilities and personnel are available for competent medical supervision. Under such circumstances, their chances for complete socio-economic rehabilitation are favorable.

RESUMEN

Para este trabajo se usó el material reunido por el autor al estudiar 200 enfermos que sufrían diabetes melitus complicada con tuberculosis. Se hace una revisión de los conceptos relativos al aumento de la susceptibilidad hacia la tuberculosis entre los diabéticos. Se discurre sobre el fondo clínico en la tuberculosis de estos individuos. Se

señalan las reglas aplicables al tratamiento de las dos enfermedades. En los casos de diabetes bien controladas, es de esperarse que los enfermos respondan de manera tan satisfactoria a las medidas usando los antimicrobianos y otros procedimientos adyuvantes, como los tuberculosos no diabéticos.

He encontrado que después de tratamiento institucional adecuado, los diabéticos con tuberculosis pueden escogerse para tratamiento ambulatorio siemore que se puedan vigilar bien. En esas condiciones sus posibilidades de recuperación socio-económica son favorables.

RESUME

Le matériel d'étude présenté dans cet article a été recueilli d'après l'expérience de l'auteur portant sur 200 malades qui étaient atteints de diabète sucré que vint compliquer une tuberculose pulmonaire. Il examine les différentes conceptions qui tentent d'expliquer l'augmentation de la sensibilité des malades souffrant de diabète sucré à contracter la tuberculose. Il discute quelques particularités du substratum clinique de la tuberculose pulmonaire chez ces individus. Il esquisse les principes thérapeutiques qui président au traitement des deux affections. Dans les diabètes bien contrôlés, les antibiotiques appropriés et des mesures complémentaires sont susceptibles de permettre un taux de guérison de la tuberculose pulmonaire qui peut être favorablement comparé à celui que l'on trouve chez les malades tuberculeux sans diabète. L'auteur a trouvé qu'après institution d'un traitement convenable, les diabétiques atteints de tuberculose pulmonaire peuvent devenir susceptibles d'être suivis à domicile, à condition qu'il y ait les facilites et la personnel nécessaire à assurer une supervision médicale. Dans de telles circonstances, leurs chances de réadaptation socio-économique complète sont favorables.

ZUSAMMENFASSUNG

Das in dieser Veröffentlichung vorgelegte Material wurde gewonnen aus der Erfahrung des Autors an 200 Patienten, die an durch Lungentuberkulose kompliziertem Diabetes mellitus litten. Es werden die Auffassungen wiedergegeben, die mit der Ursache der erhöhten Empfänglichkeit für Tuberkulose bei den an Diabetes mellitus leidenden Kranken zu tun haben. Es werden einige Besonderheiten der klinischen Substrate der Lungentuberkulose solcher Personen besprochen. Es werden die therapeutischen Richtlinien der Behandlung der beiden Krankheiten abgegrenzt. Bei gut eingestelltem Diabetes ergeben adäquate antimikrobielle und zusätzliche Massnahmen mit Bestimmtheit eine Zahl von Besserungen der Lungentuberkulose, die sehr wohl zu vergleichen ist mit derjenigen von tuberkulösen Patienten ohne Diabetes. Ich fand, dass Diabetiker mit Lungentuberkulose nach entsprechender Anstaltsbehandlung sehr wohl für eine ambulante Weiterbehandlung ausgewählt werden können, vorausgesetzt dass die Umstände günstig sind und Personal für eine ordnungsgemässe ärztliche Überwachung zur Verfügung steht. Unter solchen Bedingungen sind ihre Aussichten für eine vollständige wirtschaftliche und soziale Rehabilitation durchaus erfreulich.

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The Clinical Application of Paper Electrophoresis in Sarcoidosis*

A Preliminary Report

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We have studied the serum electrophoretic patterns in 25 patients with sarcoidosis. The electrophoretic serum analysis was made by the method of MacDonald et al,[1] normal values in paper electrophoresis are presented in Table I. The diagnosis of sarcoidosis was established in each case by clinical and laboratory studies, the biopsy showing the usual microscopic picture of non-casting epitheloid cell tubercle present in every case. The serum electrophoretic pattern of these patients with sarcoidosis is described in Table II. The electrophoretograms were characterized by an increase in the alpha 2, beta, and a marked increase in the gamma globulin, while the albumin showed a decrease. These findings were also observed by Sunderman and Sunderman[2] by Seibert and her co-workers[3] by Fisher and Davis[4] and by Harrell and Fisher.

We compared the electrophoretograms of patients with sarcoidosis with the electrophoretic patterns of the serum from 31 patients suffering from other diseases. The serum analysis of eight patients suffering from cancer of the lungs revealed a decrease in the serum albumin and an increase in the alpha 2 globulin. This was also observed in five patients with pneumonia. In five cases of tuberculous effusion and in two of pulmonary tuberculosis.

The electrophoretic patterns of the serum proteins in six patients with lymphocytic leukemias, monocytic leukemia, aleukemic leukemia and polycythemia revealed an increase in the alpha 2 globulin, and a marked reduction in the gamma globulin.

In five cases of congestive heart failure the serum analysis disclosed a reduction in the serum albumin, an increase in alpha 2 globulin and a normal gamma globulin. There were nonspecific changes in the electrophoretic serum analysis of our patients with carcinoma of the lungs, pneumonia, tuberculosis, and congestive heart failure. These changes were characterised by a reduction in the serum albumin and an increase in the alpha 2 globulin.

The mean electrophoretic patterns in our 25 patients with sarcoidosis differed from those in the above 31 cases in the following manner. The electrophoretograms were characterized by an increase in the alpha 2, the beta, and a marked increase in the gamma globulin, while the concentrations of the albumin was decreased.

The presence of a characteristic mean electrophoretic pattern in sarcoidosis can be of great help in differentiating this disease from tuberculosis, carcinoma of the lungs, and various types of lymphomas, as well as certain granulomatous conditions of known cause, such as leprosy, histoplasmosis, berylliosis and brucellosis.

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Electrophoretic patterns of the sera of eight patients with sarcoidosis were studied before, during and after treatment with cortisone and meticorten for a period of two to six months. In three cases an improvement was noted by the disappearance of respiratory symptoms and a sense of well being experienced by the patients, as well as favorable changes in the x-ray examination after three months of steroid therapy. The electrophoretograms showed a reduction in the gamma globulin components in these cases after treatment. Three treated for a period of four months

TABLE I
NORMAL VALUES OF PAPER ELECTROPHORESIS

Normal values of electrophoresis on human serum based on 20 normal adult persons:

	By per cent		By Gm. per cent
Albumin	50.0	± 5.4	3.46 Gm./100 ml. ± 0.37
a^1 globulin	5.3	± 1.6	0.37 Gm./100 ml. ± 0.11
a^2 globulin	9.6	± 2.1	0.66 Gm./100 ml. ± 0.14
B globulin	14.5	± 2.6	1.00 Gm./100 ml. ± 0.18
G globulin	20.6	± 4.5	1.42 Gm./100 ml. ± 0.31

Note: Values by weight are based on total protein determination by the biuret method.

TABLE II
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEINS IN SARCOIDOSIS

Case No.	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
			Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	7.4	2.54	0.36	0.66	1.09	2.75
2	7.8	2.46	0.37	0.61	2.02	2.28
3	7.7	3.47	0.30	0.76	1.05	2.12
4	6.4	2.80	0.28	0.80	1.09	1.43
5	7.0	2.01	0.24	0.66	1.20	2.89
6	8.	3.02	0.29	0.78	1.04	2.86
7	6.4	2.51	0.60	0.81	1.72	1.70
8	6.8	2.39	0.31	0.75	1.03	2.32
9	6.7	2.55	0.34	0.76	1.02	2.12
10	6.5	2.48	0.34	0.90	0.92	1.86
11	7.6	2.78	0.55	1.39	0.99	1.88
12	8.2	2.32	0.61	1.25	1.87	2.20
13	7.6	2.60	0.40	0.80	1.20	2.70
14	7.3	2.80	0.40	1.10	1.20	1.86
15	7.8	3.40	0.30	0.90	1.02	2.18
16	7.4	3.40	0.37	0.80	1.04	1.68
17	7.7	2.57	0.42	0.99	1.56	2.16
18	8.	2.85	0.41	.82	1.15	2.77
19	8.	2.55	0.39	1.00	1.34	2.72
20	7.4	2.88	0.27	.93	.90	2.41
21	6.7	2.89	0.33	.82	0.84	1.82
22	7.7	2.50	0.45	.80	1.20	2.75
23	7.2	2.88	0.33	1.01	1.04	1.94
24	7.2	2.85	0.40	0.90	1.20	1.85
25	7.3	2.80	0.60	1.00	1.20	1.70
Mean	7.03	2.73	0.38	.88	1.19	2.19

TABLE III
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEIN IN CARCINOMA OF THE LUNGS

Case No.	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
			Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	6.5	2.77	0.35	0.93	1.01	1.44
2	6.6	1.99	0.69	1.52	1.19	1.21
3	5.1	2.08	0.32	0.55	0.89	1.25
4	4.6	1.16	0.52	0.79	0.98	1.00
5	6.5	2.19	0.46	1.11	1.30	1.24
6	5.9	2.28	0.32	0.98	.99	1.32
7	5.6	1.69	0.45	1.01	1.18	1.25
8	6.3	2.77	0.28	0.86	0.99	1.40
Mean	5.8	2.11	0.42	0.96	1.06	1.26

TABLE IV
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEINS IN PNEUMONIA

Case No.	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
			Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	6.4	2.0	0.50	1.20	0.9	1.7
2	5.6	2.2	0.40	0.90	0.7	1.4
3	7.0	2.6	0.50	0.80	1.2	1.9
4	6.1	2.0	0.45	1.01	0.8	1.9
5	6.6	2.4	0.60	1.00	0.9	1.7
Mean	6.5	2.2	0.50	0.98	0.90	1.70

TABLE V
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEINS IN TUBERCULOUS PLEURAL EFFUSIONS AND PULMONARY TUBERCULOSIS

Case No.	Pathological Lesions	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
				Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	Pleural Effusions	8.4	2.96	0.29	1.15	0.92	3.07
2	"	6.1	2.70	0.32	0.99	0.92	1.09
3	"	6.3	2.77	0.28	0.86	0.99	1.40
4	"	6.7	2.91	0.42	0.93	1.17	1.27
5	"	6.7	2.94	0.38	0.95	1.16	1.25
6	Pulmonary Tuberc.	7.0	2.80	.40	1.5	0.9	1.4
7	"	6.4	2.90	.40	.80	1.0	1.3
	Mean	7.0	2.85	.35	1.01	1.00	1.54

TABLE VI
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEINS IN LYMPHOCYTIC LEUKEMIA AND LYMPHOMAS

Case No.	Pathological Lesions	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
				Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	Lymphosarcoma	6.1	3.13	0.44	1.38	0.58	0.54
2	"	6.6	2.90	0.49	1.11	0.96	1.13
3	Lymphocytic Leukemia	5.4	2.16	0.45	1.10	0.88	0.81
4	Monocytic Leukemia	5.5	3.00	0.28	0.42	1.07	0.73
5	Aleukemic Leukemia	6.1	2.98	0.36	0.68	0.93	1.15
6	Polycythemia	4.6	1.31	0.52	0.79	0.98	1.00
	Mean	5.7	2.58	0.42	0.91	0.90	0.89

TABLE VII
ELECTROPHORETIC DISTRIBUTION OF SERUM PROTEINS IN CONGESTIVE HEART FAILURE

Case No.	Total Protein Gm. Per Cent	Albumin Gm. Per Cent	Globulins			
			Alpha 1 Gm. Per Cent	Alpha 2 Gm. Per Cent	Beta Gm. Per Cent	Gamma Gm. Per Cent
1	6.29	2.08	0.39	1.02	0.95	1.76
2	4.69	1.49	0.24	0.77	1.48	0.91
3	5.60	2.06	0.47	0.96	1.00	1.11
4	6.20	2.70	0.40	0.90	0.70	1.50
5	6.35	2.80	0.40	0.95	0.75	1.45
Mean	5.82	2.22	0.38	0.92	1.17	1.34

with steroids showed marked improvement in symptoms, and striking changes on x-ray examination. Because of the improvement treatment was stopped. The electrophoretic pattern in these cases still showed an elevated gamma globulin. Prompt relapse occurred after discontinuing treatment in these three patients. Two with sarcoidosis under treatment with steroids presented an elevated gamma globulin and did not respond well to treatment, however, they improved on increasing the dose of meticorten. The electrophoretic pattern showed a reduction in the gamma globulin.

We feel that definite conclusions cannot be drawn at this time because the number of cases is too small and the time of observation too short.

Further studies are in progress and the results will be reported at a later date.

SUMMARY

The electrophoretic patterns of the sera of 25 patients with sarcoidosis were compared with the patterns obtained in 31 persons suffering from other diseases. Only in the cases of sarcoidosis were we able to find a characteristic mean electrophoretic pattern that is a increase in the alpha 2, beta and a marked increase in the gamma globulin while the albumin showed a decrease.

Acknowledgments: Our thanks are due to Dr. Piinn F. Morse for his help and advice. We also wish to thank Dr. R. P. MacDonald and the members of the staff for their cooperation.

RESUMEN

Los cuadros electroforéticos de sueros de 25 enfermos de sarcoidosis se compararon con los obtenidos en 31 personas que padecían otras enfermedades.

Sólo en los casos de sarcoidosis pudimos encontrar un cuadro electroforético medio consistente en aumento de las globulinas alfa 2, beta y gama en tanto que la albúmina mostró disminución.

RESUME

Les tracés électrophorétiques d'une série de 25 malades atteints de sarcoïdose ont été comparés aux tracés obtenus chez 31 personnes souffrant d'autres affections. Ce n'est que dans la sarcoïdose que l'auteur a rtouvé un tracé électrophorétique caractéristique qui se traduit par une augmentation des alpha 2-globulines, des beta-globulines et une augmentation trés nette des gamma-globulines, tandis que l'albumine se trouvait diminuée.

ZUSAMMENFASSUNG

Es werden die elektrophoretische Werte der Seren von 25 Patienten mit Sarcoid verglichen mit den Werten bei 31 Personen, die an anderen Krankheiten litten. Nur in den Fällen von Sarcoid sind wir imstande, charakteristisch elektrophoretische Mittelwerte zu erheben, nämlich eine Zunahme bei alpha 2, beta und eine beträchtliche Zunahme bei alpha 2, beta und eine bertächtliche Zunahme des Gamma-Globulins, während das Albumin eine Abnahme aufweist.

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Tuberculosis: Early Treatment

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The facts that tuberculosis is still an unconquered disease and that it continues to make considerable inroads among military personnel have been documented by Jacobs.[1, 2] He has recommended early treatment of the disease as a means of reducing its incidence and morbidity. This recommendation is supported by Waring[4] and by Myers,[5] as well as by Trimble.[10] The earliest possible recognition of the disease is considered to be by means of the tuberculin test.[11] This is made possible when a known negative reactor converts to positive. By treating such individuals before clinical tuberculosis is recognized, it is theoretically possible to destroy the bacteria during the stage of early cellular reactions in the lung, as described by Vorwald.[12] Under these circumstances, the index of successful treatment is the reconversion of the positive tuberculin test to a negative reaction. A persistent negative reaction may be interpreted to mean that the individual is not harboring living tubercle bacilli. If this theory can be applied to the intimate contacts of known clinical cases, it may be possible to reduce the incidence of clinical cases of the disease.

The authors have applied the hypothesis set forth above to a localized outbreak of the disease. Changes in assignment of the subjects and among the authors are believed to warrant publication of our observations, even though definite conclusions may not be drawn as yet.

On November 19, 1955, a soldier (J. B.) assigned to the local Finance and Accounting Detachment was found to have a moderate case of pulmonary tuberculosis.** He had been working indoors in a large room since May 20, 1955. (Figure 2) His duties brought him in daily contact with a majority of the 37 military personnel and 35 civilian employees serving in the Finance Office. In addition, the soldier occupied a room in the barracks with several others. Though he gave a history of chronic cough and a feeling of fatigue since departure from Fort Dix in May of 1955, his condition was not diagnosed until bloody sputum became his most prominent symptom. It was assumed that the soldier had tuberculosis upon arrival in the office and that all personnel working therein had undergone massive exposure for a period of six months.

This situation provided an ideal environment for an epidemiological study of the spread of tuberculosis. As a first step, all personnel working in the Finance Office were examined by means of posteroanterior chest x-ray films in November and December, 1955. Three additional clinical

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The observations and conclusions contained in this article are those of the authors and are not necessarily those of the Surgeon General, Department of the Army or any agency of the Department of Defense.

**Diagnosis confirmed, USAH, Landstuhl, Germany.

cases were brought to light and hospitalized, along with the initial patient. The fifth case was found in a soldier who had been transferred to another location a few weeks prior to the first survey. The first survey also revealed seven civilians with suspicious shadows in the lung fields. Study of these cases by the local German Public Health Service confirmed active tuberculosis in one individual and acute pneumonitis of unknown origin in another. All military cases were promptly hospitalized. Some delays were encountered in arriving at a decision concerning the civilian cases due to the complexity of administration.

The program called for re-examination of suspicious cases at three-month intervals. Due to clerical error, one additional civilian case was not confirmed until eight months after the initial survey. This person was promptly relieved from duty to await admission to a civilian hospital.

Non-suspicious individuals were re-examined six months later, in April, 1956. Thirty-four military personnel and six civilians were given first-strength tuberculin skin tests. The results showed that 16 military personnel had 1+ positive reactions. All civilian personnel were positive 1-3+. Seventeen military personnel were negative. One gave a questionably positive reaction.

Negative reactors were retested at monthly intervals. Six converted from negative to positive in May and June 1956. The question of whether or not these converters should receive treatment while on the job was a matter for much discussion and consultation with expert phthisiologists.

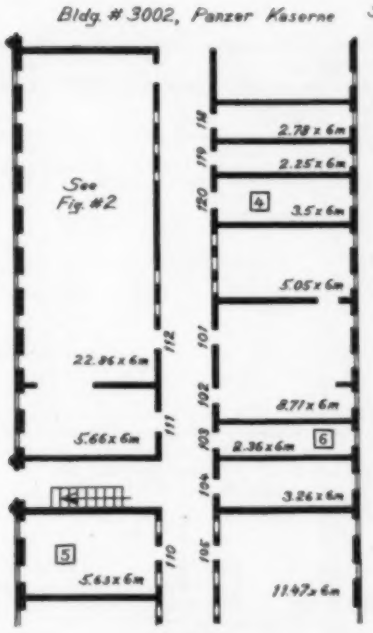

FIGURE 1

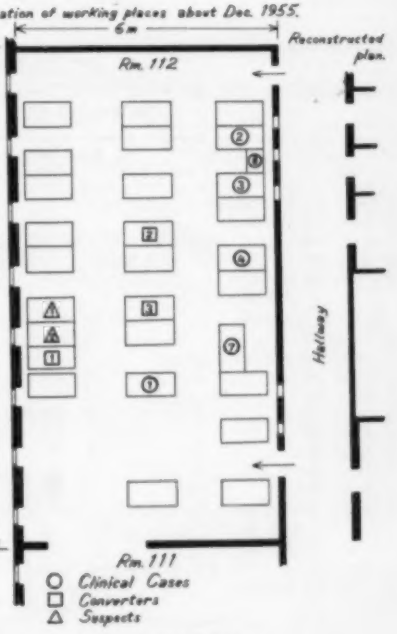

FIGURE 2

Clinical cases are numbered in order of their sequence of diagnosis. Cases 5 and 6 worked outside the office space shown in the above diagram.

Because of the known massive exposure, authority to treat the converters was granted. Accordingly, treatment with streptomycin and isoniazid was begun in July, 1956. The course of each individual is set forth in the following Tables, Figures 3 through 8.

FIGURE 3—CASE I

J. I. WHITE MALE, AGE 23. INTIMATELY EXPOSED TO J. B. (SEE FIG. 2) FOR PERIOD OF 6 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
30 Nov. 55	Normal					
13 Apr. 56	Normal					
17 Apr. 56		neg (1st str)				
11 June 56		1+ (1st str)	2 mm/hr			
20 June 56				100 mgm, 3xday		1 gm, 2xweek
9 July 56	Normal			↓		↓
19 July 56			3 mm/hr			
30 July 56			2 mm/hr			
16 Aug. 56		1+ (1st str)				
18 Aug. 56			1 mm/hr	↓		
23 Aug. 56				100 mgm, 3xday	6 gms/day	Discontinued
30 Aug. 56				↓	10 gms/day	
Returned To ZI					↓	

Follow-up report, Regional Office, Veterans Administration, Newark 2, New Jersey, 13 May 1957: No medication. Chest x-rays: free of pathologic change. PPD skin tests: not done. Veteran is in excellent general health.

FIGURE 4—CASE II

G. M. WHITE MALE, AGE 24. INTIMATELY EXPOSED TO J. B. (SEE FIG. 2) FOR A PERIOD OF 2 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
12 Dec. 55	Normal					
5 Apr. 56	Normal					
17 Apr. 56		neg (1st str)				
28 May 56		1+ (1st str)				
8 June 56	Normal PA & Apical					
18 June 56			1 mm/hr			
20 June 56				100 mgm, 3xday		1 gm, 2xweek
19 July 56			2 mm/hr	↓		↓
30 July 56			2 mm/hr			
18 Aug. 56			1 mm/hr			
23 Aug. 56				100 mgm, 3xday	6 gms/day	Discontinued
30 Aug. 56				↓	10 gms/day	
8 Sept. 56					12 gms/day	
9 Sept. 56					6 gms/day	
11 Sept. 56	Normal PA & Apical				↓	
11 Oct. 56		1+ (1st str)	4 mm/hr			
26 Nov. 56	Normal		3 mm/hr	↓		
28 Dec. 56			1 mm/hr	Discontinued (on own initiative but started both again)	Stopped	
13 Feb. 57	Normal	neg (1st str)				
13 Mar. 57		2+ (2nd str)		100 mgm, 3xday	Stopped	

FIGURE 5—CASE III

D. R. WHITE MALE, AGE 27. INTIMATELY EXPOSED TO J. B. (SEE FIG. 2) FOR A PERIOD OF 6 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
28 Nov. 55	Normal					
16 Apr. 56	Normal					
17 Apr. 56		neg (1st str)				
28 May 56		1+ (1st str)				
8 June 56	Normal PA & Apical		4 mm/hr			
20 June 56				100 mgm, 3xday		1 gm, 2xweek
19 July 56			2 mm/hr	↓		↓
30 July 56			2 mm/hr			
23 Aug. 56		neg (1st str)		100 mgm, 3xday	6 gms/day	Discontinued
29 Aug. 56		1+ (1st str)			10 gms/day	
30 Aug. 56					12 gms/day	
8 Sept. 56					6 gms/day	
11 Sept. 56	Normal PA & Apical		3 mm/hr		↓	
11 Oct. 56					Discontinued	
26 Nov. 56	Normal				use on own	
28 Dec. 56			3 mm/hr	Discontinued on own but started again		
7 Feb. 57	Normal		3 mm/hr			
17 Mar. 57 Rotated* To ZI						

*Follow-up report, US Army Hospital, Fort Ord, California, 15 May 1957: Felt completely well, had no symptoms of any sort, either pulmonary or general in nature. Taking isoniazid, 100 mgm TID. Chest x-ray is negative. Sedimentation rate 17. PPD, first-strength, 2+.

FIGURE 6—CASE IV

C. T. WHITE MALE, AGE 22. INTIMATELY EXPOSED TO GERMAN CASE (SEE FIG. 1) FOR PERIOD OF 6 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
28 Nov. 55	Normal					
15 Mar. 56	Normal					
17 Apr. 56		neg (1st str)				
28 May 56		neg (1st str)				
9 July 56	Normal	1+ (1st str)				
30 July 56	Normal					
[illegible]	Apical					
4 Aug. 56				100 mgm, 3xday		1 gm, 2xweek
6 Aug. 56			3 mm/hr	↓		↓
23 Aug. 56					6 gms/day	Discontinued
30 Aug. 56					10 gms/day	
8 Sept. 56					12 gms/day	
11 Sept. 56	Normal PA & Apical		2 mm/hr		↓	
26 Nov. 56	Normal		4 mm/hr			
3 Dec. 56		1+ (1st str)		↓		
28 Dec. 56			1 mm/hr	Discontinued on own initiative but started again		
8 Jan. 57	Normal					
7 Feb. 57			3 mm/hr			
Rotated To ZI						

Follow-up report, Regional Office, Veterans Administration, Seattle 1, Washington, dated 5 June 1957: Chest x-ray taken April 26th shows no evidence of pulmonary pathology. Further skin testing has not been done. The veteran's general health as of late April was excellent.

FIGURE 7—CASE V
R. W. WHITE MALE, AGE 27. INTIMATELY EXPOSED TO J. B. (SEE FIG. 2) FOR A PERIOD OF 6 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
28 Nov. 55	Normal					
5 Apr. 56	Normal					
17 Apr. 56		neg (1st str)				
28 May 56		1+ (1st str)				
8 June 56	Normal PA & Apical		5 mm/hr			
18 June 56			3 mm/hr			
20 June 56				100 mgm, 3xday		1 gm, 2xweek
19 July 56			4 mm/hr	↓		↓
30 July 56			1 mm/hr	↓		↓
16 Aug. 56		1+ (1st str)		↓		↓
18 Aug. 56			1 mm/hr	↓		↓
23 Aug. 56				↓	6 gms/day	Discontinued
30 Aug. 56				↓	10 gms/day	
8 Sept. 56				↓	12 gms/day	
11 Sept. 56	Normal PA & Apical		5 mm/hr	↓	↓	
26 Sept. 56				↓	Stopped on own	
11 Oct. 56		1+ (1st str)	6 mm/hr	↓		
26 Nov. 56	Normal PA & Apical		3 mm/hr	↓	12 gms/day	
25 Jan. 57				↓	↓	
7 Feb. 57	Normal		5 mm/hr	↓	Discontinued	
13 Feb. 57		neg (1st str)		↓		
13 Mar. 57		2+ (2nd str)		↓		
18 Apr. 57				Stopped on own initiative but started again		

FIGURE 8—CASE VI
D. P. WHITE MALE, AGE 31. INTIMATELY EXPOSED TO J. B. (SEE FIG. 2) FOR A PERIOD OF 6 MONTHS

Date	Chest X-ray	Skin Test	Sedimentation Rate	Isoniazid	PAS	Streptomycin
28 Nov. 55	Normal					
17 Apr. 56		neg (1st str)				
11 June 56		neg (1st str)				
25 June 56	Normal	1+ (1st str)				
2 July 56	Normal Apical		2 mm/hr	100 mgm, 3xday		1 gm, 2xweek
17 July 56				↓		tingling lips Tingling generalized ½ gm, 2xweek
30 July 56			2 mm/hr	↓		↓
14 Aug. 56			1 mm/hr	↓		↓
23 Aug. 56				↓		Discontinued
6 Sept. 56				↓	6 gms/day	
13 Sept. 56	Normal PA & Apical		1 mm/hr	↓	↓	
11 Oct. 56		neg (1st str)		↓		
22 Oct. 56		3+ (2nd str)		↓		
28 Nov. 56	Normal			↓		
2 Jan. 57			3 mm/hr	Discontinued on own initiative but started again		
8 Feb. 57	Normal					
13 Apr. 57 Rotated To ZI		neg (1st str)				

Follow-up report, United States Army Hospital, Fort Benning, Georgia, 29 August 1957: Examined in the Medical Clinic 27 June 1957. Discontinued tuberculosis chemotherapy April 1957. Denies all symptoms referable to active disease. Chest x-ray, apical lordotic view, 27 June: negative. Sedimentation rate: zero. CBC: normal. PPD No. 1: normal. PPD No. 2: markedly positive, no slough. Physical examination normal with appearance of good health.

Discussion

The foregoing experiences led the authors to be in complete agreement with Jacobs'[12] opinion concerning the ever-present threat of this disease. The advisability of initial and periodic chest x-ray film for all personnel, especially those whose work confines them to offices, is confirmed once again. It is believed that the value of early discovery of chest pathology is worth the risk of possible mutations from radiation. Follow-up examinations of these 72 individuals have led to the discovery of nine clinical cases.* The last military case, found in October, 1956, was that of a soldier whose tuberculin reaction was positive at the first testing in April 1956, and therefore was not placed upon treatment. Unfortunately, there is no way of knowing when his initial infection may have occurred.

The experience and deductions therefrom does not include a series of completely valid controls. The 16 military personnel who had normal chest films and initial tuberculin tests of 1+ six months after discovery of the initial case may be considered as partial controls. As mentioned above, one of these soldiers developed clinical tuberculosis 11 months after the first case was discovered. In addition, the 12 military personnel whose chest films have remained normal and whose tuberculin tests are still negative may be looked upon as a control group in some respects. It is assumed that the degree of exposure of this latter group was considerably less than that experienced by the six converters. The six converters were not divided so as to provide a control group because of the degree of exposure as shown in Figures 1 and 2. Under these circumstances, the risk was considered to be too grave. If treatment forestalled the development of a single clinical case, the program of therapy was exceedingly worthwhile.

Initial therapy with streptomycin and isoniazid was well tolerated in all but one case. In August 1956, the authors were advised to discontinue streptomycin and to place the converters on para-aminosalicylic acid. All six individuals experienced difficulty in taking 10 and 12 grams of this drug on a daily basis. Amphojel had no beneficial effect on the symptoms of gastric uneasiness, diarrhea, or constipation. As shown in the case charts, the dose of PAS was reduced to 6 grams, and finally discontinued altogether. Isoniazid alone presented no untoward effects until March, 1957, when the two cases remaining under direct observation of the authors began to complain of vague gastric uneasiness. After six months of treatment, the men became less interested in continued cooperation and began to stop medication on their own initiative. Energetic advice at frequent intervals was necessary to get them to take the medicine again. The original plan called for therapy for one year. As each man left the office, for return to the continental United States, he was strongly advised to continue under medical observation for a period of at least one year. A letter was forwarded to the medical facility where each man expected to receive further medical care, asking for cooperation and timely reports.

It is suggested that therapy for such cases will be more certain and therefore more effective with streptomycin alone, or in combination with isoniazid, since the individual will be required to visit the medical facility at more frequent intervals. With streptomycin, it will be definitely known that the medication was actually received. In a military situation, it is advisable to shorten the period of treatment for such cases because of changes in assignment by reason of military necessity. A six-month period of treatment with streptomycin and isoniazid is suggested.

It should be pointed out that several other preventive measures were applied to this situation. All bed clothing used by military personnel of the Finance Office who slept in the barracks was disinfected and exchanged for new items. All rooms which had been occupied by clinical cases were disinfected thoroughly on three separate occasions. The office rooms and equipment were likewise disinfected on three occasions and a strong battery of ultraviolet lights was used in the rooms all night for one month. The large room (Figure 2) was cubiclized and two ventilating fans were installed. Additional office space was obtained to relieve the crowded condition. All personnel were given more time for exercise in the out-of-doors. An orientation film on tuberculosis was shown to all personnel. The possible effects of these measures cannot be estimated, nor can they be completely overlooked.

Conclusions

An experience with a localized outbreak of 10 clinical cases of tuberculosis among 38 military and 35 German civilian personnel, all serving in a finance office during 19 months of observation, is described. The discovery of six individuals whose tuberculin skin test converted from negative to positive and their treatment on a duty status is also documented.

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*Two additional civilian cases of old tuberculosis, which have become active, were discovered in May and June of 1957 as a result of continued study of all personnel in the Finance Office.

SUMMARY

Tuberculosis is still a disease of military importance. Early recognition and treatment are necessary to minimize its incidence and morbidity. Initial and periodic chest x-ray films, as well as tuberculin tests, are of great value in the discovery and prevention of infection with tubercle bacilli. The possible development of mutations does not warrant the neglect of chest x-ray films even when it may be necessary to repeat them at frequent intervals.

Treatment of tuberculin converters before clinical signs are evident is believed to be warranted in the presence of known massive exposures. Effective therapy can be given in an on-duty status. Reactions of 1+ to first-strength tuberculin may return to negative under therapy. Reactions to second-strength tuberculin are likely to be positive after first-strength reactions have become negative. Under ideal circumstances, converters should be followed periodically until the second-strength reaction has been negative for at least one year.

RESUMEN

La tuberculosis es aún una enfermedad de importancia militar. Se necesita su descubrimiento temprano y pronto tratamiento para disminuir al mínimo su incidencia y la morbilidad. Son de gran valor las radiografías de tórax inciales y periódicas para el descubrimiento y prevención de la infección. El desarrollo de mutaciones posibles no justifican el que se descuide la radiografía de tórax y aún puede ser necesario repetirlas a intervalos frecuentes.

El tratamiento de los que han virado su reacción a la tuberculina antes de que aparezcan signos clínicos, se cree que se justifica cuando hay exposiciones múltiples conocidas. La terapéutica efectiva puede hacerse sin que se abandone el servicio. Las reacciones de grado 1 plus a la primera dilución de tuberculina, pueden virar a la negatividad después del tratamiento. Las reacciones a la segunda concentración, es posible que sean positivas después de que las reacciones positivas a la primera dilución se hayan tornado negativas. Bajo condiciones ideales, los que han virado su reacción a positiva deben observarse periódicamente hasta que la segunda concentración se haya hecho negativa durante un año por lo menos.

RESUME

La tuberculose est encore une affection d'importance dans l'armée. Le dépistage et le traitement précoces sont nécessaires pour réduire au minimum sa fréquence et sa gravité. Des clichés thoraciques au début et ensuite périodiquement répétés, ainsi que des tests tuberculiniques. sont d'une grande valeur dans la découverte et la prévention de l'infection par le bacille tuberculeux. La fréquence possible des changements d'affectation ne justifie pas que l'on néglige les radiographies thoraciques, même s'il est nécessaire de les répéter à des intervalles fréquents.

Les auteurs pensent que le traitement des individus qui font leur virage de réactions tuberculiniques alors qu'il n'y a encore aucun signe clinique est une notion de contage important. Un traitement efficace peut être mis en oeuvre tout en laissant l'individu à son service. Des réactions faibles à la tuberculine (+) à forte dilution peuvent redevenir négatives sous traitement. Des réactions à la tuberculine de moins forte dilution peuvent être encore positives alors que les réactions à la tuberculine de faible dilution sont devenues négatives. Dans des conditions idéales, les individus qui ont viré leurs réactions tuberculiniques devraient être suivis périodiquement jusqu'à ce que les réactions à la tuberculine à faible dilution aient été négatives pendant au moins une année.

ZUSAMMENFASSUNG

Die Tuberkulose ist auch jetzt noch eine Krankheit von militärischer Wichtigkeit. Frühzeitige Erkennung und Behandlung sind notwendig, um ihr Auftreten und ihre Morbidität auf das kleinstmöglichste Ausmass herabzusetzen. Anfängliche und periodische Thoraxröntgenaufnahmen sind ebenso wie Tuberkulinprüfungen von grossem Wert für die Entdeckung und Verhinderung der Infektion mit Tuberkelbazillen. Die mögliche Entwicklung von Mutationen ist keine Rechtfertigung für die Geringschätzung von Lungenröntgenaufnahmen, selbst wenn es nötig sein sollte sie im häufigen Intervall zu wiederholen.

Von der Behandlung der Tuberkulin-Konvertoren, ehe klinische Anzeichen augenfällig werden, wird angenommen, dass sie berechtigt ist bei Vorliegen von bekannter beträchtlicher Exposition. Effektive Therapie kann auch während der Zeit der Dienstpflicht gegeben werden. Reaktionen von 1+ auf Tuberkulinimpfstärke I können unter der Behandlung wieder negativ werden. Reaktionen auf Stärke II des Tuberkulin bleiben wahrscheinlich positiv, nachdem die Reaktion auf Stärke I negativ geworden ist. Unter idealen Umständen soll man die Konvertoren periodisch solange überwachen, bis die Reaktion auf Stärke II wenigstens 1 Jahr lang negativ geblieben ist.

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Bronchography without Oil and Iodine — The Use of Barium as a Contrast Medium

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Bronchography was brought into use only after the presentation of lipiodol by Sicard and Forestier[12] in 1921. None of the former trials to opacify the bronchial tree had succeeded in clinical practice because the contrast media, then used, were not completely harmless. For about 25 years lipiodol was widely used throughout the world as the elective agent for bronchography, thanks to the excellent x-ray pictures one could get with it. The disadvantages of lipiodol were not clearly grasped at that time because this product, as it has no free iodine in its molecule, does not irritate the respiratory mucous membrane and therefore permits the patients to tolerate the examination well. On the other hand, until the end of World War II, the horizons of bronchography were limited due to the slow progress of thoracic surgery. Nowadays, however, with the routine practice of pulmonary resections, particularly in tuberculosis, bronchography has become an indispensable method of establishing an anatomical and topographical diagnosis of bronchial lesions.

The increasing indications for bronchography, imposed by the growing demands of modern pulmonary surgery, made the harmful effects of lipiodol better known. Briefly, they are connected to the physical properties of the product and to its capacity of injuring tissues. In the first place, we have to mention the reduced viscosity of the iodized oil, which causes it to reach quickly the pulmonary periphery, causing a rapid and useless filling of the bronchoalveolar units and masking the fundamental elements of radiological diagnosis. On the other hand, the so-called alveolar filling with lipiodol is unfortunately of long duration, the lung being "tattooed" for several months afterwards, thus making the study of the radiological evolution of each case difficult. Besides, it makes impossible other bronchographic studies and increases the functional risk of pulmonary surgery by the implicit ventilatory restriction. The toxic aggressions to the organism are resumed in the general manifestations of iodism, hyperthermia and local formation of oil granulomas. The disintegration of the lipiodol molecule with liberation of iodine happens in an alkaline medium and therefore it is not attacked by the gastric juice but by the intestinal juice.[8] In the lungs, there is practically no absorption or disintegration of lipiodol, either by phagocytosis or by lipodieresis. In reality, only a fraction of the contrast medium introduced into the bronchial tree is retained in the pulmonary parenchyma. The greater part is gradually expectorated or swallowed, being either decomposed in the bowel or absorbed and eliminated through the kidneys. Consequently, the iodism can only happen when lipiodol is swallowed; it is a rare complication, although sometimes severe. Hyperthermia is a common finding after bronchography with iodized oil,

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but has no clear explanation until this date. Moreover, the local antiseptic role attributed to the opaque substance could not be demonstrated.[8] The prolonged permanence of the agent in the lung causes chronic foreign body type reactions, the so-called oil granulomas. Such parenchymatous lesions can always be demonstrated, according to Fischer,[5] after the stasis of iodized oil in the lung for more than three months. Studying the local pulmonary reaction to lipiodol in surgical specimens, Felton[4] found iodized oil microscopically demonstrable in 62 per cent of cases, and in these 26 per cent had oil granulomas.

The disadvantages of lipiodol having become known, several investigators began the search for new and better contrast media for the bronchi. The researches were oriented into two directions: first, the substitution of the oil as the vehicle for the iodine (water-soluble contrast substances in a viscous medium); and second, increase of the viscosity of lipiodol (mixture with sulphanilamide crystals).

The water-soluble iodine salts, largely used in angiography, are of no use in bronchography since, being too fluid, they are entirely dispersed after a few breathing movements. In 1948 Morales and Heiwinkel[9] contoured the issue adding to the aqueous opaque medium a macromolecular substance, the carboxymethylcellulose, capable of increasing its viscosity manifold, retarding thus considerably the dispersion of the opaque medium in the bronchial tree. Peck *et al.*[10, 11] changed the carboxymethylcellulose molecule for that of methylcellulose (Methocel-diodrast), based on the fact that the latter, in clinical and experimental studies, is "essentially nontoxic," when administered into the vein[7] or by mouth.[1] The water-soluble compounds, in viscous media, did not succeed in becoming the ideal agents for bronchography due to several basic defects: 1) they are hypertonic substances, therefore extremely irritating to the tracheobronchial mucosa, causing coughing, broncho- and laryngospasm; this necessitates a very deep local anesthesia, which adds to the risks of the toxic manifestations of the iodine, those caused by the anesthetic agent; 2) in order to obtain good radiological records, it is necessary to use the technic of selective bronchography through the Métras catheter, which reduces the simplicity of the examination; 3) the simultaneous opacification of both lungs is not practicable due to the great quantity of contrast agent used, since its highly viscous nature may cause a severe respiratory obstruction; 4) the radiological image lacks the density or the definition obtained with lipiodol, specially in the lateral views; besides, it is also necessary to work faster due to the rapid absorption of the substance into the bronchial system, the opaque medium (iodine) is "washed out" from the viscous medium (carboxymethylcellulose), being absorbed and eliminated by the kidneys; due to this fact, after a short interval there is no longer the faintest trace of contrast medium in the films of the thorax, but a portion of the substance which accounts for the viscosity is retained for weeks, being gradually eliminated by the ciliary action and by expectoration; around these residues of carboxymethylcellulose, foreign-body granulomas may be formed.[13]

The second line of research was nothing but a return towards lipiodol, through the correction of its main disadvantage, namely its low viscosity. This was attained through a combination of lipiodol with powdered sul-

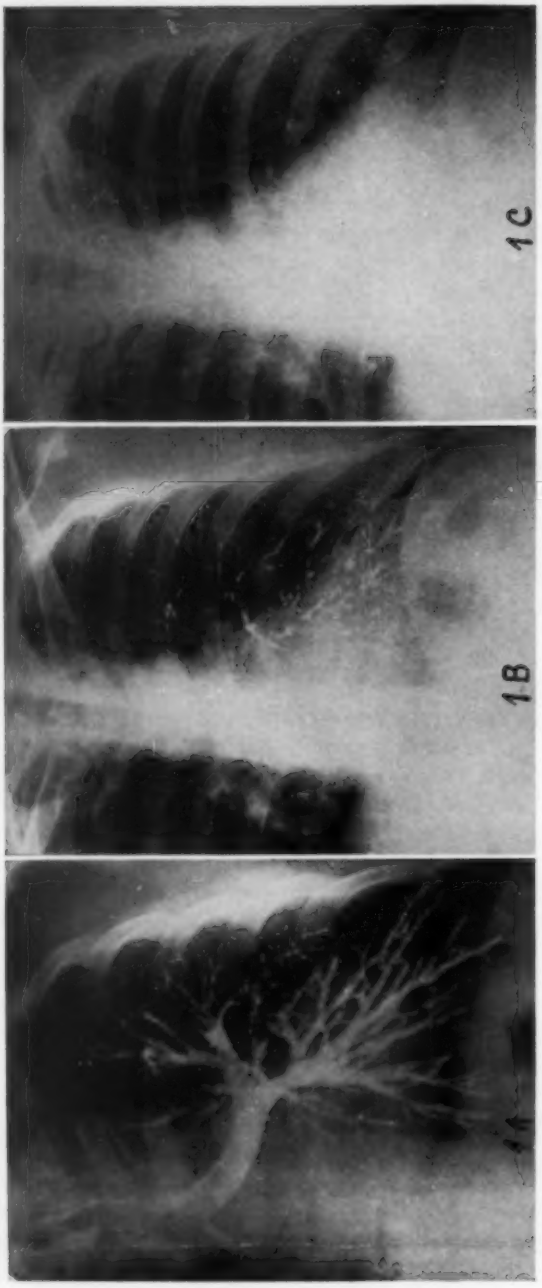

FIGURE 1A: Left bronchogram.—FIGURE 2B: Residual contrast medium in the bronchi, after coughing and expectoration by the patient, at the end of the examination.—FIGURE 1C: X-ray film taken three days later, showing total absence of the contrast medium.

phanilamide, an association advised as early as 1945 even though with a different finality (to combat bronchial infection),[3] and specifically proposed in 1951 to avoid alveolar impregnation by Houghton and Ramsay.[6] It is our opinion, based on a five year experience, that lipiodol thickened with sulpha crystals constitutes an excellent preparation for bronchographic use, giving the beautiful radiologic images of the simple iodized oil without its main disadvantage, the quick and persistent alveolar filling. However, in this brief paper on the methods of opacifying the bronchi, two unfavorable aspects of the above-mentioned mixture can not be forgotten: the increase of potential toxicity of the contrast medium by incorporating a sulpha radical, and its high commercial cost.

Recently, Di Rienzo and Duarte[2] suggested a third solution to the problem when they demonstrated the possibility of obtaining good contrast of the bronchial system with the barium suspensions in carboxymethylcellu-

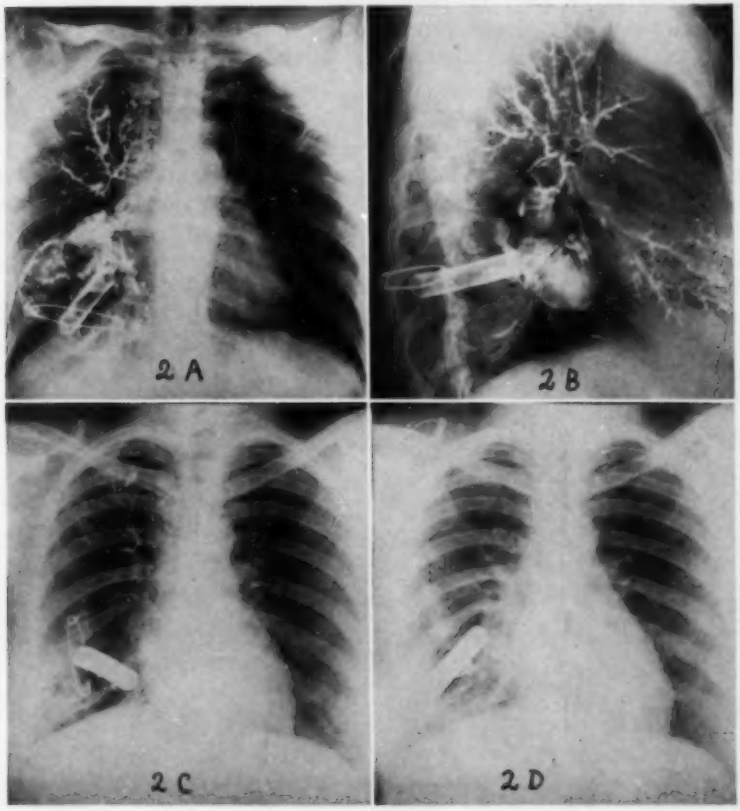

FIGURE 2: Right bronchogram in a case of pulmonary abscess of the lower lobe, surgically drained.—*Figure 2A and 2B:* Front and profile x-ray films, showing presence of drained cavity in the lower lobe. The upper and middle lobe bronchi are normal.—*Figure 2C:* X-ray film taken 24 hours later. A small residue of contrast medium can be noticed in small bronchi.—*Figure 2D:* Total absence of opaque medium, five days later.

lose used in gastrointestinal radiology. In their paper, however, there is no information concerning either the dosage and concentrations of the viscous medium and the opaque substance, or the vehicle used.

We pursued this matter further, convinced of the potential advantages of this idea, and tried to develop it in practice by starting with the products for radiodiagnosis existing in the Brazilian trade. We began with those in which the barium was associated with a macromolecular substance, capable of maintaining a permanent suspension when mixed with an aqueous vehicle, thus avoiding the tendency of the barium particles to agglutinate, forming a solid concretion after the water evaporated. Initially, we used the compound proposed by the Argentine authors (carboxymethylcellulose and barium), which presents itself as a jelly. Soon we found out that its viscosity was low with the consequent alveolar impregnation and permanence of the contrast medium in the pulmonary parenchyma for several weeks, well corroborated in one case where pneumonectomy was performed. We then turned our attention to a similar product, presented in a powdered form, in which the carboxymethylcellulose was substituted by the methylcellulose, the Celobar,* with the following composition:

Barium Sulphate, pur. .....150 g.
Methylcellulose ..... 2 g.

In our opinion, the use of Celobar in a powdered form seemed to have the advantage of altering the viscosity of the contrast medium, increasing as well as decreasing it, through different proportions of the aqueous vehicle.

*Prepared by Química Farmacêutica Maurício Villela, S.A., Rio de Janeiro.

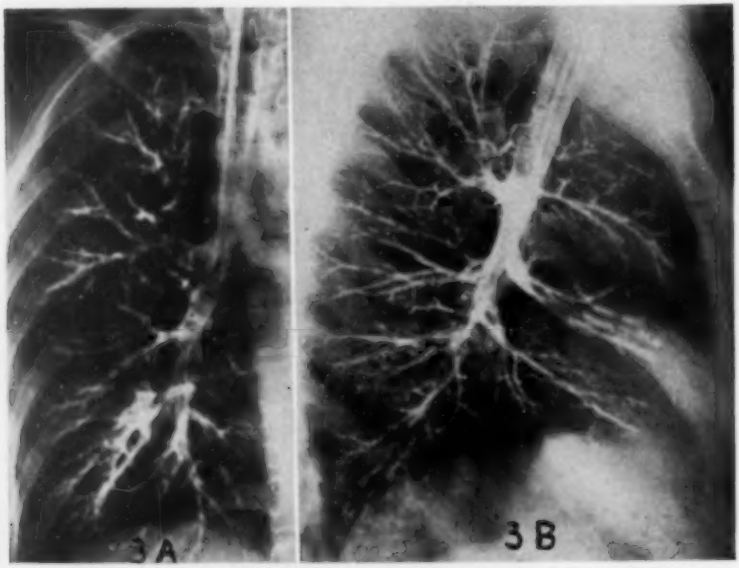

FIGURE 3: Bilateral simultaneous bronchogram in a case of middle lobe syndrome.—*Figure 3A and 3B:* Right bronchograms with front and profile views. In the latter, there are cylindrical bronchiectasis in the retracted middle lobe.

In the course of our studies, we concluded that the adequate formula for bronchography with barium, to guarantee the opacification of the whole bronchial tree without impregnating the alveoli, should be:

Celobar .....20 g.
Physiologic saline solution .....30 ml.

The above amounts of Celobar and physiologic saline solution are placed in a beaker and thoroughly mixed with a glass rod, resulting in a homogeneous colloidal suspension, appropriate for endobronchial use. The physiologic saline, as a vehicle, is superior to distilled water because of its isotonicity.

The bronchographic technic which we employ consists of the following steps: pre-medication with luminal and atropine, topical anesthesia of the respiratory tract with pontocaine in a 1 per cent solution, tracheal intubation with a French catheter and introduction of the contrast medium with the patient in a lateral decubitus on the x-ray table, on the side to be examined. We inject the barium suspension with a common glass syringe in a dosage of 20 ml. into the side to be opacified first and 10 ml. into the opposite side, when simultaneous bilateral bronchography is indicated. The contrast medium fills progressively the whole pulmonary canalicular system, including the delicate bronchi in the periphery of the organ, without penetrating into the bronchoalveolar units. The tolerance by the patient is perfect and in the absence of coughing the opaque mass remains stagnated in the bronchial tree, allowing an unhurried, quiet and careful radiologic examination; the seriograph, if not available, can be dispensed with. When the examination is finished, the patient is ordered to cough and to expectorate, the greater part of the contrast medium thus being eliminated. In the majority of the cases, already in the third day there is no more opaque substance in the lungs, and when there is, it is present in the lumen of the small bronchi, from which it is removed by the ciliary action and

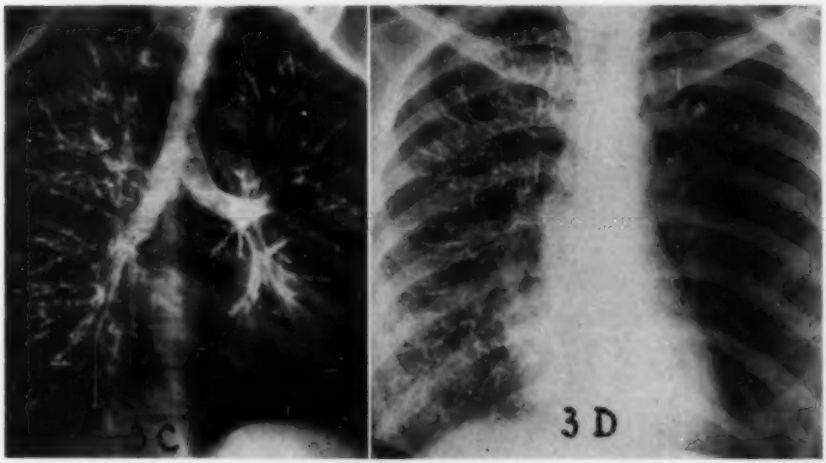

FIGURE 3C: Bilateral bronchogram.—FIGURE 3D: X-ray films taken 24 hours after bronchography, showing the residue of contrast medium in the small bronchi, which will be removed in the following days by coughing and by ciliary action.

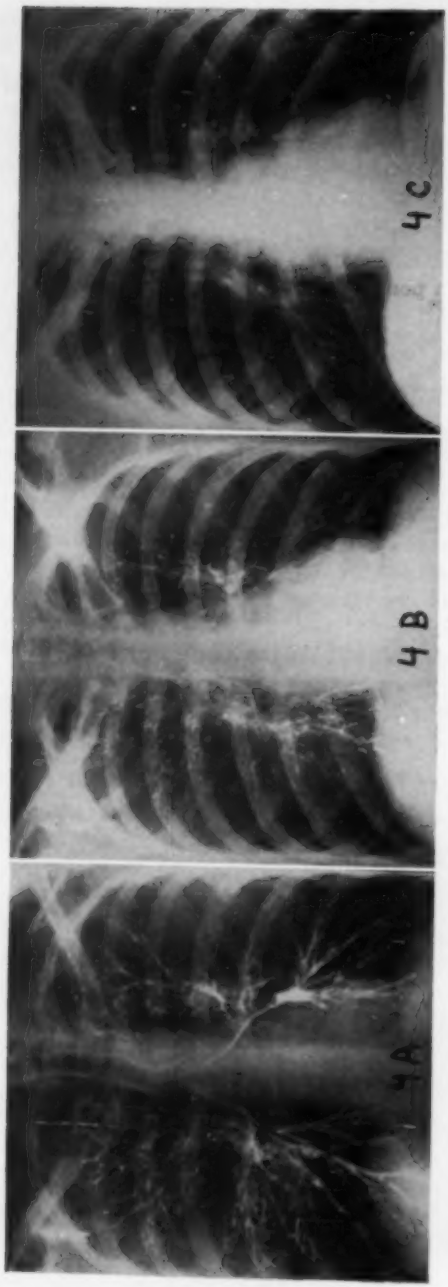

FIGURE 4A: Normal bilateral bronchogram (notice the delicate relief of the mucous membrane of the trachea and bronchi).—FIGURE 4B. Residual contrast medium in the air channels, after coughing and expectoration by the patient, at the end of the examination.—FIGURE 4C: X-ray film taken two days after bronchography, showing total elimination of the contrast medium.

coughing. We have never observed a complication either during or after the examination, in 25 patients in whom we tried this new type of contrast medium.

In brief, the association of barium sulphate with methylcellulose, in a colloidal suspension and in the above mentioned concentrations, offers several important advantages over the other agents used in bronchography:

1) It is an association of inert and non-toxic substances, a compound which when swallowed is eliminated with the feces, as demonstrated by the long experience acquired through its use in gastrointestinal radiology.

2) It does not cause local irritation when put in contact with the respiratory mucous membrane.

3) It gives excellent radiologic images of the air channels, not through the filling of their lumen, but through the coating of their mucosa, showing clearly its relief.

4) It goes as far as the delicate bronchi of the pulmonary periphery, without penetrating into the bronchoalveolar units.

5) It is easily eliminated from the organism, without suffering any alteration of its structure. This means that in this colloidal suspension barium and methylcellulose are closely associated, the opaque medium being unable to be "washed out" from the viscous medium. Consequently, when the thoracic x-ray films fail to show opaque substance, this is an unmistakable sign that there is also no more viscous medium in the lungs.

6) And lastly, a financial advantage: it is much cheaper than lipiodol or the water-soluble iodinated products.

Figures 1, 2, 3 and 4 illustrate the quality of the bronchograms obtained with the new opaque medium.

Addendum: Since August 1957 when this paper was submitted for publication, we have performed over 200 bronchographic examinations with barium as described above and obtained the same excellent results herein reported. Attention should be drawn to the fact that Celobar being a very hygroscopic powder, it is absolutely necessary that this product should be kept dry in order to be used efficiently, always being preserved from external humidity. This is the only way of getting an adequate viscous suspension after application of the formula advised in the present article.

SUMMARY

After a critical study of the different contrast media in current use in bronchography, the advantages of replacing them with a compound of barium sulphate and methylcellulose, using physiologic saline as a vehicle are emphasized. In the dosage and concentration recommended, the product opacifies the whole bronchial tree, without penetrating into the alveoli, and is readily eliminated by ciliary action and by coughing. Besides these advantages, it has proved in 25 clinical cases to be an entirely non-toxic agent, well tolerated by the respiratory mucous membrane and extraordinarily cheaper than the other products used in bronchography.

RESUMEN

Después de hacer un estudio de los medios de contraste habitualmente usados para la broncografía, se hacen notar las ventajas de substituirlos por un compuesto de sulfato de bario y metilcelulosa usando como vehículo la solución salina fisiológica. A la dosis y a la concentración recomendadas, el producto opacifica el árbol bronquial completo sin penetra en los alveolos y es fácilmente eliminado por la acción ciliar y por la tos.

Además de estas ventajas, se ha demostrado en 25 casos clínicos que se trata de un agente completamente atóxico, bien tolerado por las mucosas respiratorias y extraordinariamente más barato que los otros productos usados en broncografía.

RESUME

Après une étude critique des différents milieux de contraste dans la pratique courante en bronchographie, l'auteur met l'accent sur les avantages qu'il y a à les remplacer

par un composé de sulphate de baryum et de méthylcellulose, utilisant le sérum physiologique comme excipient. Au dosage et à la concentration recommandée, le produit opacifie l'arbre bronchique complet, sans pénétrer dans les alvéoles, et il est rapidement éliminé par l'action ciliaire et la toux. En dehors de ces avantages, il s'est montré chez 25 malades examinés un agent nullement toxique, bien toléré par la membrane muqueuse respiratoire. Il est infiniment moins couteux que les autres produits utilisés en bronchographie.

ZUSAMMENFASSUNG

Nach einer kritischen Überprüfung der verschiedenen laufend bei der Bronchografie gebräuchlichen Kontrastmittel werden die Vorzüge betont, sie durch eine Verbindung von Barium-Sulfat und Methylzellulose unter Verwendung von physiologischer Kochsalzlösung als Vehikel zu ersetzen. In der empfohlenen Dosierung und Konzentration gibt das Mittel eine Verschattung des gesamten Bronchialbaumes, ohne in die Alveolen einzudringen, und wird prompt ausgeschieden durch die Wirkung der Cilien und den Husten. Abgesehen von diesen Vorzügen hat es sich in 25 klinischen Fällen als gänzlich untoxischer Stoff erwiesen, der von der respiratorischen Schleimhaut gut vertragen wird und ausserordentlich viel billiger ist, als die anderen bei der Bronchografie angewandten Mittel.

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Treatment of Pulmonary Tuberculosis with Isoniazid and Pyrazinamide: Experience in 114 Cases

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Pyrazinoic acid amide, now commonly known under the name Pyrazinamide or PZA and in previous years as Aldinamide, is a nicotinic acid derivative chemically related to isonicotinic acid hydrazide, more commonly designated Isoniazid or INH. A review of the early laboratory studies of PZA is omitted because of space limitations. In brief these studies indicated PZA alone to be a drug of slight to moderate anti-tuberculous activity and to be potentially hepatotoxic.

New impetus was given to further studies with PZA when it was demonstrated by McCune and Tompsett[1] that the combination of PZA and INH together produced an antimicrobial action which was qualitatively different from that produced by any of the standard anti-tuberculosis drugs administered either singly or together. By the microbial enumeration technique these authors demonstrated that unlike previous anti-tuberculosis drugs used singly or in combination which produced a depressed but stabilized population of bacilli in the spleens of infected animals, with PZA-INH treated animals, the census of the population of tubercle bacilli did not stabilize but instead continued to fall at a rapid rate until bacilli could no longer be detected in the spleens or lungs of any of the animals. Indeed, the effects produced by PZA-INH were of a much more eradicative type than those produced by other drugs, and conceivably, may have represented complete sterilization of the treated animals.

Further confirmation of the unusual additive effects of PZA and INH was provided by the intracellular studies of Mackaness[2] who showed that PZA and nicotinamid, which are almost devoid of tuberculostatic activity against tubercle bacilli grown under ordinary cultural condition, possessed a high level of activity against tubercle bacilli, strain H37Rv, grown in isolated rabbit monocytes *in vitro*. Compared with INH, PZA was found to have only a slow bactericidal effect upon intracellular bacilli under these conditions, but when combined with isoniazid, PZA resulted in an increase in the bactericidal effect of isoniazid.

Review of Previous Clinical Studies

Yeager and co-workers[3] studied PZA when used alone in the treatment of 43 patients. A rapid and satisfactory symptomatic response was obtained in febrile patients but the beneficial effects were transient and apparently limited by the rapid emergence of drug resistant bacilli, particularly in patients with far-advanced tuberculosis with large cavities. The toxic reactions noted during the administration of the drug were all mild and consisted of two cases of jaundice, and other cases showing joint pains, eosinophilia, palpitation, chills and fever. Following discontinuation of PZA, jaundice reached a peak after a few days, then slowly receded. Tests of liver function suggested parenchymal involvement, which slowly cleared. Six and eight months after termination of treatment there were no residual signs of hepatic disease.

The major advance in our knowledge of PZA and the current revival of interest in this drug may be attributed to the extensive studies of McDermott and his group.[4-6] These workers investigated the antituberculous effect produced by PZA and INH

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in a series of related studies in animals and man and concluded that this drug combination exerts a high degree of antituberculous action *in vivo* of a sort superior and qualitatively different from that of current antituberculous drugs used either singly or together. Fifty-five patients were treated with PZA in a total daily dosage of 50 mg. per kg. and INH in a total daily dosage of 5 mg. per kg. This combination was given for three months or longer and isoniazid alone thereafter. This regimen resulted in a sustained reversal of infectiousness in 90 per cent, substantial roentgenographic improvement in 75 per cent and closure of all cavities in 65 per cent of those with cavitary lesions. These results were obtained within the first six months of therapy (except for later cavity closure in two patients). No patient showed progression of disease on roentgenography. Hepatotoxicity consisted of one fatal drug-induced hepatitis on the 55th day of therapy and five instances of non-fatal hepatitis. It was concluded that INH-PZA exerts antituberculosis activity *in vivo* of a sort superior to that of the other current antituberculosis drugs but it was felt that the high incidence of hepatitis in man made use of this regimen, at least in the dosage used in the first reported study,[4] inadvisable as a treatment for tuberculosis.

Campagna and co-workers[7] treated 21 patients with PZA and INH. Persistent sputum "conversion" occurred in all but two of them. Mild jaundice appeared briefly for approximately one week in three. Unlike all other investigators who have worked with PZA, these investigators "believed that this combination of drugs lends itself readily to treatment of far-advanced tuberculosis on an ambulatory basis."

Schwartz and Moyer[8] reported a two and one half year experience with PZA, used both alone and together with SM, PAS or INH. PZA used alone was found to be an effective drug in the treatment of pulmonary tuberculosis, although for only a short time. When used together with SM or PAS, PZA did not enhance the effectiveness of these drugs or delay the emergence of PAS resistance or SM resistance to tubercle bacilli. PZA with INH, however, was found to be a highly effective regimen. As regards roentgenographic improvement and cavity closure it was the equal of any combination of SM, PAS or INH. However, as regards bacteriological conversion without concurrent favorable x-ray change, and as regards the relative absence of worsening roentgenographically, the findings were striking. Thus in 10 out of 30 cases tuberculous cavities did not close by x-ray film evidence although longstanding bacteriological negativity was achieved. One hundred per cent of patients were negative at the eighth month and this achievement "in spite of the fact that cavities persisted in a considerable proportion of patients, indicated a high degree of continuing antibacterial action." In a total of 181 patients treated with PZA, either alone or in combination with other drugs, over a period of two and one half years, it was necessary to discontinue PZA-INH in two because of mild jaundice. Only one showed worsening roentgenographically and in none did INH resistance develop. The low incidence of jaundice encountered in this series prompted the recommendation that the combination of PZA and INH be used more widely in the treatment of tuberculosis, particularly in SM resistant cases.

Hepatotoxicity of PZA was studied in a United States Public Health Service Cooperative Clinical Investigation.[9] Six hundred and eighty seven patients were distributed among three treatment regimens: INH plus 25 mg. PZA per kg., INH plus 40 mg. PZA per kg. and INH plus PAS. This was a relatively short term study, the total period of PZA administration being 12 to 24 weeks; however, it is striking that no significant hepatic toxicity was noted in this study.

Ewart and Roye reported[10] liver toxicity with INH-PZA in three of 65 patients. These authors expressed the opinion that the low incidence of serious liver toxicity

TABLE I
ROENTGEN EVALUATION AT 4 MOS.
INH-susceptible—MA & FA
58 cases

No change	8
Slight improvement	10
Moderate improvement	17
Marked improvement	22
Worse	1
	58
Cavity persisted but negative	11
Late reopening of cavity (8th and 13th mo.)	2

in this study was due to the performance of liver function studies every two weeks. It was also felt that "any doubts about toxicity are overbalanced by the clinical response which has been as stimulating and exciting as any regimen used since the early introduction of SM."

The results of INH-PZA therapy in 376 patients in the Veterans Administration-Armed Forces Cooperative Chemotherapy Study[11] were recently summarized. Of the 376 patients, four developed jaundice and 29 an elevated bromsulfalein retention; 24 were reported as "hepatitis, liver damage, or PZA toxicity." It was noted that liver toxicity occurred twice as frequently in the group over 50, as in the group under 50 years of age. In original treatment, and in retreatment cases, PZA-INH was noted to exceed, at four and at eight months, intermittent SM plus daily INH and intermittent SM plus daily PAS in achieving marked or moderate x-ray improvement, reversal of infectiousness, and cavity closure. PZA-INH, and INH-PAS appeared to be of more nearly equal therapeutic efficacy as measured by these three criteria, with PZA-INH slightly superior in some instances, and never inferior. PZA appeared to be effective in preventing the development of resistance to INH. The results obtained in the treatment of far-advanced disease are considered particularly worthy of mention. Similar to the experience of Schwartz and Moyer[8] and to our own experience, marked or moderate improvement roentgenographically five to eight months after start of chemotherapy was essentially identical (68 to 71 per cent) in the four groups receiving SM-INH, SM-PAS, INH-PAS, and INH-PZA; but the percentage of cases negative on culture in these four respective groups was 44, 48, 52 and 63 per cent. This type of result[5, 11] is interpreted as indicating the superiority of INH-PZA in effecting bacteriological negativity despite persistence of cavity and/or appreciable residual infiltration.

Allison[12a] utilized half the customary dosage of INH and PZA, namely 1.5 gm. PZA daily, and 150 mg. INH daily in an effort to overcome the hepatotoxicity of PZA and possibly retain the beneficial effect of this combination. One patient of 69 receiving INH-PZA became jaundiced, four others developed abnormal liver function tests. "It is believed from this study that pyrazinamide and isoniazid in the low dosage used, and under the careful observation pursued with liver function tests before treatment and every two weeks during treatment, is an excellent regimen for short period treatment (not over eight months) in those who are not chronic alcoholics, who have never had liver disease, and who can be treated in hospital."[12b]

In an early study of PZA given concurrently with SM and/or PAS Phillips and coworkers[13] observed one case of hepatitis and five with slightly abnormal liver function tests in a total group of 29. The PZA was stopped only in the one with hepatitis, and in one with abnormal liver function tests; otherwise the medication was continued without ill effect. Phillips and Horton[14] later studied the combination PZA-INH and compared it with INH-PAS. In this study bromsulfalein and cephalin flocculation tests were done at monthly intervals. At the fourth month of therapy the roentgenographic results were essentially identical in the two groups but substantially more of the patients on INH-PZA were negative on culture at this point, 82 per cent as compared with 67 per cent on INH-PAS. At the eighth and 12th month the differences were no longer significant. Like the experiences of Schwartz and Moyer[8] not a single incidence of the emergence of INH resistance occurred in the INH-PZA group. From the fact that a somewhat greater proportion of patients treated with INH-PAS required collapse or resectional measures (15 per cent as compared with 11 per cent) it was concluded that PZA-INH was a slightly more effective regimen. Among 38 receiving INH-PZA there were two cases of jaundice and three developed rise in BSP retention, two of these after one year of therapy. Similar to the finding of other investigators[7] cephalin flocculation tests did not parallel the abnormalities noted with BSP retention tests.

TABLE II

BACTERIOLOGICAL EVALUATION

Treated at least 4 mos., INH-susceptible, MA & FA

55 cases

Mo. of conversion	Cases	
1	36	80%
2	8	
3	4	13%
4	3	
Remained positive	4	7%
—INH resistant in 2 mos.	4	

Materials and Methods

One hundred and fourteen patients have been treated with the combination of INH 300 mg. daily and PZA 3.0 gm. daily (a smaller number in the study later received 1.5 gm.) for periods of one to 25 months. Criteria for inclusion in the study were—1) all were original treatment with reference to PZA and—2) they were either original treatment with INH or, if retreatment with reference to this drug, were shown by laboratory studies to still be susceptible to INH.

Except for three women, they were all men ranging from 21 to 76 years. The racial distribution was 33 Negro and 81 White. All had a BSP retention not exceeding 7 per cent in 45 minutes prior to PZA administration. This determination together with cephalin flocculation, thymol turbidity, complete blood count, and routine urinalysis were repeated twice each month. A significant elevation in BSP retention which was confirmed by prompt repetition of the test was the signal for discontinuation of PZA. It was not uncommon to find elevations up to 16 per cent in 45 minutes, which, on a repeat test within 24 hours, yielded a result within normal limits; other investigators have communicated similar experiences. Serum alkaline phosphatase levels were determined concurrently with the BSP test for a period of six months at which time the test was abandoned because of the observation that it did not show abnormalities as frequently as the BSP test.

The diagnosis of pulmonary tuberculosis was confirmed bacteriologically in all cases except three in whom previous therapy of less than two weeks duration or minimal extent of lesion made bacteriological confirmation impossible. Chest roent-

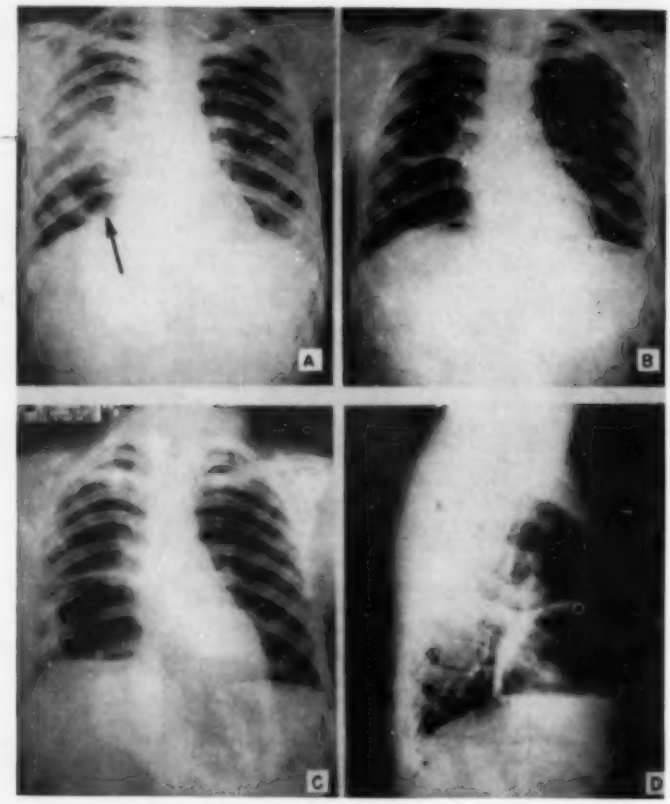

FIGURE 1A: Start of INH-PZA therapy, October 14, 1954. Note large cavity in right middle lobe.—FIGURE 1B: May 23, 1955, excellent clearing of pulmonary infiltrations with loss to view of right middle lobe cavity; this was confirmed on anteroposterior as well as lateral tomograms.—FIGURE 1, C and D: November 4, 1955, reopening of right middle lobe cavity with fluid level but continued negative bacteriology. PZA was discontinued July 5, 1955, and INH alone maintained.

genograms and sputum, gastric or tracheal specimens for bacteriological study were repeated at monthly intervals. Susceptibility tests were carried out on all positive cultures obtained for susceptibility to SM, PAS and INH.

Patients were chosen by a method of random selection based on the final digit of the hospital register number, and received either INH-PAS, INH-PZA or, later in the study, INH-Cycloserine.

Results

Roentgen evaluation of this combination was restricted to moderately advanced and far advanced cases and was made at the fourth month of treatment. Fifty-eight cases met these criteria and the results are summarized in Table I. Only one showed worsening during the first four months. Two showed late reopening of cavity at the eighth and 13th month of therapy respectively, the PZA having been discontinued in the latter four months earlier, but both remained negative by sputum and gastric examinations despite reappearance of cavity. One such case is illustrated by figures 1 and 2.

This young Negro with extensive disease involving his entire right lung and a large cavity in the right middle lobe (Fig. 1*A*) was placed on INH-PZA therapy October 14, 1954. All smears and cultures became negative for tubercle bacilli dur-

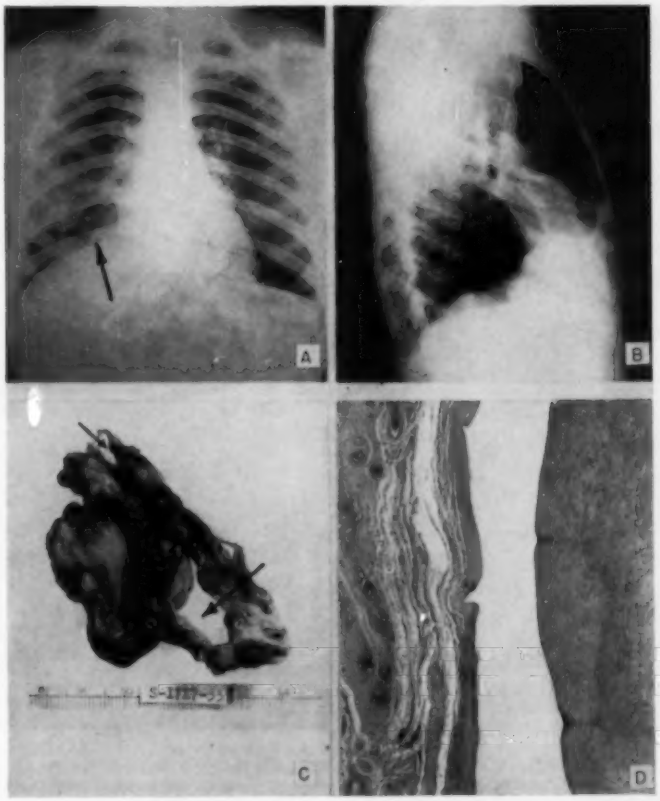

FIGURE 2, A and B: December 14, 1955, spontaneous decrease in size of right middle lobe cavity with continued negative bacteriology repeatedly.—FIGURE 2C: Resected right middle lobe showing large, smooth, clean right middle lobe excavation.—FIGURE 2D: Microscopic section of right middle lobe cavity showing open healing without residual specific evidence of tuberculosis.

ing the first month of therapy and there was rapid clearing of pulmonary infiltrations with loss to view of the right middle lobe cavity (Fig. 4B) on antero-posterior, lateral tomograms, and conventional films. Because of the excellent result obtained, PZA was discontinued July 5, 1955, and the patient thereafter treated with INH alone. Four months later he complained of slight malaise and indisposition, and for a few days afternoon temperature reached a peak of 99.4°F, but there was no increase in cough or expectoration and numerous sputum, tracheal and gastric specimens all returned negative, at first on smear of concentrated specimen and later on culture. Chest film at this time (Fig. 1C) showed huge ballooning of the right middle lobe cavity with fluid level. Other diagnoses considered at the time were bronchopleural fistula with localized pyopneumothorax, loculated spontaneous hydropneumothorax and pulmonary cystic disease unrelated to original tuberculous cavity. Without therapy other than continuation of INH alone, fever subsided in a few days and successive serial chest x-ray films showed spontaneous decrease in the size of the right middle lobe excavation (Figs. 2, A and B). Despite continued negative bacteriological examinations and a roentgenographic course again appearing favorable, resectional surgery was advised for fear of the potentialities of an imperfectly healed cavity in the right middle lobe and the possibilities of recurrence of ballooning and fluid retention in the future. The

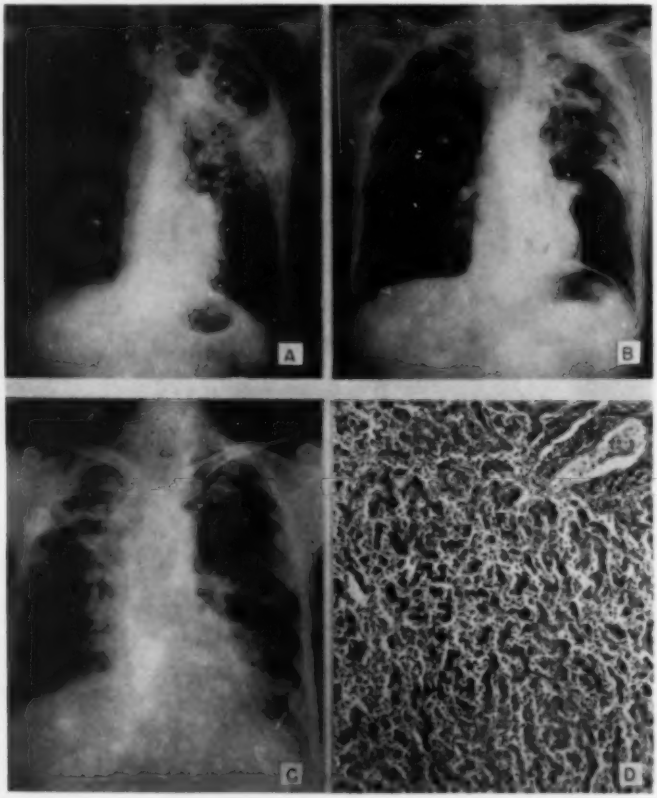

FIGURE 3A: December 21, 1954, start of INH-PZA therapy.—FIGURE 3B: March 15, 1955, regression of infiltration and decrease of cavity size but persistence of positive sputum and development of INH resistance in 2 months of INH-PZA therapy.—FIGURE 3C: INH-PZA started December 27, 1954, in patient positive for many years and resistant to SM. X-ray of April 7, 1957, shows persistent open, negative cavity in right upper lobe and essentially unchanged x-ray appearance despite bacteriological negativity since the first month of INH-PZA therapy. PZA was discontinued in this case on January 21, 1957, and patient thereafter maintained on INH-PAS with continued negativity.—FIGURE 3D: Liver of patient dying with jaundice after six weeks of PZA therapy. Note extensive cellular infiltration but complete absence of necrosis of liver cells. Role of PZA questionable.

findings at the operative table confirmed the clinical impression of a tension cavity in the right middle lobe. Grossly (Fig. 2C) the wall of the cavity was completely clean and smooth and microscopic examination (Fig. 2D) confirmed the impression of pathological open healing.[25]

Twenty-two of the 58 cases showed marked, 17 moderate, and 10 slight improvement at the four month observation point (Table I). Most of those in the slight improvement group fell into the moderate or markedly improved stage at the eighth and 12th month observation points.

Eight patients showed no change but it should be stressed that three of these had chronic longstanding fibroid or productive-type involvement that would not be expected to resolve under any drug regimen and 5 of the 8 had a large cavity which persisted open but there was prompt "conversion" to negative bacteriological status which has persisted to date, even after discontinuation of the PZA for periods of 13 to 21 months. In other words while the x-ray evaluation of these eight cases was "no change," the bacteriological result in all 5 was prompt "conversion," and 5 of these 8 have been discharged to normal activity in their community with continued satisfactory status on follow-up examinations. One such case is illustrated by figure 3C.

He had had chronic pulmonary tuberculosis with positive sputum for many years. He had become resistant to SM. On INH-PZA there was prompt "conversion" which has been maintained for 37 months despite persistence of open cavity and an essentially unchanged x-ray film appearance.

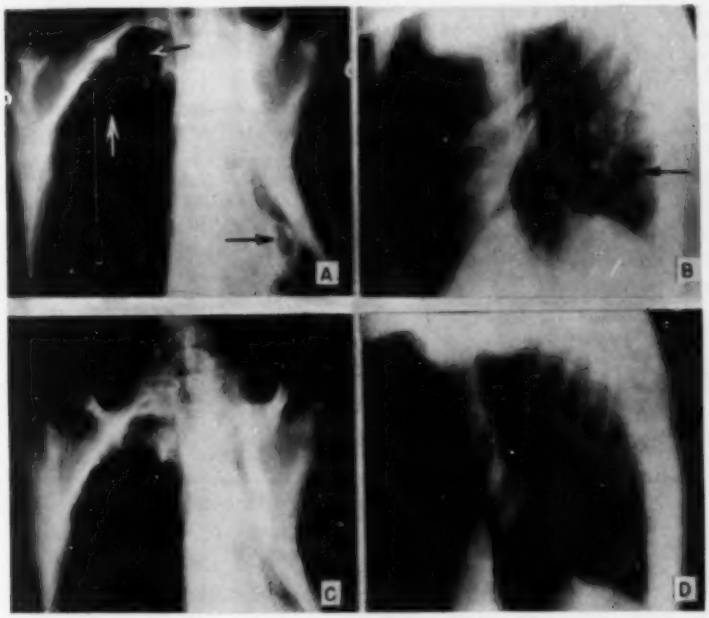

FIGURE 4, A and B: January 3, 1955, Anteroposterior and left lateral tomograms illustrating multiple cavities in right upper lobe and cavities in posterior basal segments of left lower lobe under thoracoplasty. At this time patient had been continuously positive for at least 5 years, and was fully resistant to SM-PAS.—FIGURE 4, C and D: April 5, 1955, AP and lateral tomograms illustrating loss to view of cavities in both lung fields. "Conversion" occurred during the first month of INH-PZA therapy and has persisted to date. PZA was discontinued after 16 months on May 14, 1956, and patient maintained on INH alone since then.

TABLE III
BACTERIOLOGICAL EVALUATION
CAVITARY COMPONENT 4 CM. OR MORE
19 cases

Closed and neg.	25 to 37 mos.	4
Open and neg.	14 to 35 mos.	11
Open, positive, resistant		4

Closure of large cavities under INH-PZA occurred less frequently than persistence of open cavity with negative bacteriological status as is seen in Table III. A rather striking example, however, of cavity closure under this drug regimen is illustrated by figure 4.

This 33 year old diabetic patient had cavities replacing the right upper lobe, and a large cavity under a left thoracoplasty done in 1949 (Fig. 4 A, B). These cavities with persistently positive sputum had been present for a Veterans Administration Hospital documented period of five years, during which time all susceptibility tests indicated resistance of the patient's tubercle bacilli to SM and PAS. INH had been withheld in previous years because of some observations in this patient in 1952, that it tended to provoke diabetic acidosis. Following a bronchospirometric examination in January, 1955, carried out for the purpose of planning a possible bilateral surgical program for coping with this patient's longstanding chronic disease, the patient unfortunately had a marked spread of infiltration into the right lower lung field and became acutely and severely ill with high fever and toxicity. Because of the desperate situation INH was cautiously started parenterally without the patient's knowledge. There was no aggravation of the diabetic state, the dosage was rapidly increased to 300 mg. daily with PZA, sputum converted during the first month of therapy and there was rapid clearing of the fresh pulmonary infiltrations in the right lower lung field and rapid loss to view of the cavities in both lung fields (Fig. 4 C, D). INH-PZA therapy was maintained in this case for a period of 16 months until May 14, 1956, at which time the PZA was discontinued and the patient maintained on INH alone. On repeated re-examinations the inactive state has been maintained to date.

Bacteriological evaluation at the fourth month of therapy is summarized in Table II, and was restricted to those with moderately or far advanced lesions in whom the diagnosis of tuberculosis was bacteriologically proved prior to therapy and whose bacilli were shown to be susceptible to INH. Fifty-five of the 58 patients utilized for the roentgen evaluation in Table I, met these criteria. It is noted that 80 per cent of this group achieved conversion in the first two months of treatment while the great majority

TABLE IV
HEPATOTOXICITY
EVALUATED IN 114 CASES

Duration of treatment — 1 to 25 mos.		
Abnormal BSP only	16*	
Abnormal SAP only	1	15%
Abn. BSP and jaundice and/or hepatomegaly	3**	
Abn. BSP and "hepatic symptoms"	1	4%
Questionable hepatic death	1	
Total hepatotoxicity	22	19%

*1 case receiving Constarch with PZA
*2 cases receiving PZA 1.5 gm. daily
*Liver biopsy in 1 case neg. with BSP 44%, SAP 20 U
**1 case receiving Thorazine with PZA

did so during the first month, and an additional 13 per cent converted during the third or fourth month of therapy, giving an overall conversion rate of 93 per cent in four months. It appears from our data that if bacteriological conversion is going to occur under this drug regimen it does so during the first month of treatment in the majority of cases, and if it does not occur after four months of treatment, persistence of a positive state and development of INH resistance is to be expected. Four cases, 7 per cent, remained positive, and all four of these cases became resistant to INH after two months of treatment; they were all cases with total cavitary component measuring 8 cm. or more. With the single exception of worsening noted in Table I, the other three open positive resistant cases all continued to show satisfactory regression of pulmonary infiltrate despite the persistence of cavity. One such case is illustrated in figure 3 A, B.

This 65 year old white man was treated with INH-PZA beginning December 16, 1954. Although there was satisfactory roentgenographic clearing, sputum remained positive and susceptibility study on sputum specimen of February 19, 1955, later revealed a 3 plus growth on the tube containing 1 gamma of INH per ml. with a 4 plus growth on the control tube. On the sputum specimen of April 11, 1955, the 1 gamma tube showed a 4 plus growth, the 5 gamma tube showed a 3 plus growth, with 4 plus growth on the control. PZA was discontinued on March 24, 1955, because of a completely asymptomatic rise in BSP retention to 22 per cent. INH was then administered with PAS until May 3, 1956, during which time there was gradual decrease in pericavitary infiltration but persistence of cavity and positive sputum, and on May 3, 1956 under protection of original treatment SM and Terramycin,® left pneumonectomy was successfully carried out with satisfactory control of disease.

An interesting, and we believe somewhat unique, occurrence with INH-PZA therapy is the high percentage of open negative cavities obtained. This is illustrated in Table III, in which all cases with a cavity 4 cm. or larger were classified as to fate. It is seen that of 19 such cases, four closed and have remained so for periods of 25 to 37 months, four remained open, positive and became INH resistant, but 11 remained open and negative on all smears and cultures for periods of 14 to 35 months.

A limited experience with INH-PZA therapy in patients who had previously received INH and whose bacilli had become INH-resistant was, as expected, discouraging both as to roentgen and bacteriological results.

TABLE V
TIME OF APPEARANCE OF HEPATIC TOXICITY

Mo. of Rx	No. of Cases
½	1*
1	3
2	3
3	4
4	1
5	2
6	3**
7	2
8	2a
10	1
	22

each * = 1 case of jaundice and/or hepatomegaly
each a = anorexia, nausea, etc.

Thus of nine such patients treated with INH-PZA for four months or longer, three showed progression by roentgenogram and three showed no change; the others showed only slight improvement. Bacteriologically, eight remained positive and only one, whose bacilli showed a 3 plus growth on INH-containing culture media as compared to a 4 plus growth on control medium, "converted" in two months.

The major and really only drawback to INH-PZA therapy is the hepatotoxicity of PZA. This is summarized in Table IV. In 114 cases under treatment for one to 25 months, treatment had to be discontinued in 16 because of an asymptomatic rise in BSP retention; in one, the serum alkaline phosphatase (SAP) rose while BSP was normal, although in a series of consecutive parallel determinations it has been our experience that the BSP retention is a more sensitive index of PZA hepatitis than SAP level. Three had unequivocal clinical evidence of hepatitis in addition to abnormal liver function studies, and one had a rise in BSP with slight anorexia and nausea. One became jaundiced after being on PZA for six weeks and died within 48 hours. His liver, however, showed only cellular infiltration and no necrosis (Fig. 3D), and liver cell necrosis to our knowledge has been a uniform finding in all other fatal cases of PZA hepatotoxicity of which personal communication indicates approximately five or six cases have occurred to date. This case moreover had had extensive surgical procedures

TABLE VI

	Total cases	Cases with jaundice and/or hepatomegaly	Per Cent	Cases with abnormal function tests and/or symptoms	Per Cent	Remarks
Yeager[5]	43	2	4.7			
McDermott et al.[4]	55	4*	7.3	2	3.6	*1 fatality
Muschenheim et al.[6]	61	2	3.3			"Low-dosage" PZA
Campagna et al.[7]	21	3	14.2			
Schwartz and Moyer[8]	181	2	1.1	3	1.7	
U.S. Public Health Service[9]	(est.) 458	0	0			
Potter and Chang[1]	61	8*	13.1			*1 fatality PZA alone
Ewart and Roye[10]	65	1	1.5	2	3.1	
VA-Army-Navy[11]	376	6	1.6	51	13.6	
Schwartz, J.[2]	58	2	3.4	1	1.7	
Phillips et al.[12]	29	1	3.4	5	17.2	
Phillips and Horton[14]	38	2	5.3	3	7.9	
Allison[13]	69	1	1.4	4	5.8	"Low-dosage" PZA
Small	114	5*	4.4	17	15.0	*1 fatality —PZA etiology doubtful
TOTALS	1,629	39		88		

1. Potter, B. P. and Chang, S. F.: *Dis. of Chest*, 27:44, 1955.
2. Schwartz, J. A.: Tr. 15th VA Conf., p. 115, 1956.

including multiple blood transfusions, and whether this death with jaundice is truly a PZA death remains doubtful. The other figures are also weighted on the heavy side since they include in the abnormal liver function group one case who was receiving Constarch, a known hepatotoxic drug, concurrently with PZA, and in the clinical toxicity group one who was receiving Thorazine with PZA. It is interesting to note that two showing liver function abnormalities were receiving only 1.5 gm. PZA daily, and that liver biopsy in one of these cases was negative at time liver function studies were markedly abnormal. Upon withdrawal of the PZA, there was a rapid return to normal hepatic function tests both in the group with clinical hepatic involvement, and in the group showing only abnormal liver function tests.

The time of appearance of hepatotoxicity is analyzed in Table V, and shows no predilection for any time period, with the possible exception that no toxicity was detected in any of 12 cases receiving PZA for more than 10 months and as long as 25 months. Our sickest case of clinical hepatitis occurred in the patient receiving INH-PZA for only two weeks.

Discussion

From our experience with INH-PZA therapy of pulmonary tuberculosis during a period of a little over 3 years in 114 patients, we agree fully with the observations of McDermott and his group[4-6] that this form of therapy is qualitatively and quantitatively of a nature superior to that of hitherto used combinations of SM-INH-PAS. An examination of our data and that of other investigators summarized in the first part of this paper lends considerable support to this impression. Thus in the combined data of the VA-Army-Navy[11] it is noted when the results at five to eight months of therapy in the far-advanced group are evaluated that while roentgenographic evaluation was almost identical in the four drug regimens (SM-INH, SM-PAS, INH-PAS, and INH-PZA), the per cent of cases negative on culture in this same group of cases was 44, 48, 52 and 63 per cent in these four respective regimens. Likewise Schwartz and Moyer,[8] in an experience with 181 patients treated with INH-PZA over a period of 2½ years, emphasized the attainment of negative cultures in all patients at the eighth month of therapy in spite of the fact that cavities persisted in a considerable proportion of patients. Allison[12] has made similar observations of the bacteriological effect of this drug combination.

It is felt that the currently conventional method of evaluating effectiveness of an antituberculosis drug regimen which is based on inter-regimen comparisons of degrees of improvement roentgenographically and, as a rule, bacteriological evaluation within those groups, is not a fully adequate measure for evaluating a regimen such as INH-PZA which appears to have an eradicative action bacteriologically superior to currently used drug regimens, but without a corresponding superiority in effecting roentgenographic improvement. This is particularly well seen from the data of Table I, in which eight of 58 patients are listed as showing no change. This would ordinarily be construed, considering that these patients all had moderately or far-advanced disease, as a poor result, when in fact all eight achieved bacteriological "conversion," with five of the eight achieving such conversion despite the persistence of open cavity. This type of bacteriological result is also emphasized in Table III, in which it is seen that with cavities 4 cm. or more, many more open negatives, 11, were obtained than cavity closures, 4, by this therapy. It is suggested that further studies of INH-PZA if carried out, or re-evaluation of previous data, analyze in greater detail the bacteriological results in the "no change" or "persistent cavity" group, particularly as compared with the more conventional evaluations.

If the bacteriological superiority of INH-PZA is granted, the questions regarding hepatotoxicity naturally arise: 1) Are there apparent reasons for the wide differences in reported hepatotoxicity (Table VI); 2) What measures might be taken to minimize hepatotoxicity or to predict impending danger in this respect; 3) Is the superiority of the regimen such that even a low incidence of hepatotoxicity justifies its retention as a therapeutic method? As can be seen in Table VI, definite clinical hepatic involvement is reported to occur during INH-PZA therapy in from 0 to 7.3 per cent of the cases treated. It is felt that the figures of Campagna[7] and Potter and Chang can not be considered for comparative purposes with the other figures listed, since in the former, three cases of jaundice are reported without significant abnormalities in liver function tests and jaundice cleared during continued PZA therapy, both of these features being unique in the experience of the total group of investigators of this problem. Potter and Chang obtained their results with the use of PZA alone

in a highly select and poor risk type of patient. This still leaves us with a spread ranging from 0 to 7.3 per cent of clinical hepatotoxicity. In an effort to see if these differences might be associated with the frequency with which hepatic function tests were carried out during PZA administration, we found that it was difficult to ascertain from the published data precisely how often such tests were done. But we were impressed by the fact that the lowest figures for clinical hepatic toxicity were obtained by those workers[9, 10, 12] who specifically stated that liver function tests were carried out at intervals of every two weeks or less; in the U.S. Public Health Service Study,[9] liver function studies were carried out at weekly intervals, with no toxicity in several hundred patients. Both Ewart and Roye[10] and Allison[12] carried out liver function tests every two weeks and stressed the importance of such frequent tests to prevent hepatotoxicity. This corresponds well with our own experience which has been that abnormalities of liver function appear suddenly, not stepwise, and practically all significant test abnormalities appeared in patients who had returned a perfectly normal test one-half month earlier. Phillips and Horton[14] who, on the other hand, report an interval of one month between routine liver function studies encountered a significantly higher incidence of hepatotoxicity than the workers mentioned above.[9, 10, 12] Certainly this appears to be a clue worth further study and if recent reports of the superior value of serum transaminase level in detecting early liver damage[16-18] are confirmed, it is possible that these tests which can easily be carried out at weekly intervals might go a long way toward preventing clinical hepatic involvement by PZA. The experience of Muschenheim et al[4] "that the standard liver function tests were not helpful in detecting liver damage until it became apparent clinically" is quite at variance with the experiences of most other investigators who, on the contrary, have consistently found a much higher percentage of abnormal liver function tests than of clinical liver damage.

In three of our patients BSP determinations had to be abandoned because of the development of allergy to bromsulfalein, and from this standpoint alone tests such as the various transaminases[16-18] should be most useful.

In our own experience and that of many other investigators[7, 10, 14] the cephalin flocculation test is by no means useful for detecting damage due to PZA. In addition we have shown[19] a high incidence of abnormal cephalin flocculation tests to occur in the course of pulmonary tuberculosis without any evidence of accompanying liver disease, probably associated with changes in the serum proteins described electrophoretically in uncomplicated pulmonary tuberculosis.

If the specter of hepatic toxicity can be eliminated by new and improved, or more frequent, tests of liver function, the question may justifiably be raised as to what type of clinical situation would warrant using a drug with *any* potential for serious damage when other drugs without such dangers are available. From a careful review of the literature and our own data our reply to this question would be that this drug regimen is well worth utilizing, even in the face of a small degree of risk, in the type of situation where one is likely to have only one chance to achieve bacteriological "conversion." We refer to the type of case with far advanced, large-cavitary type of involvement, in the advanced age group with pulmonary emphysema and bilateral involvement, who is not a suitable candidate for any form of surgery, and in whom one would not confidently expect long-term bacteriological "conversion" by SM-PAS but possibly by INH-PAS or triple drug therapy. From an analysis of our data, particularly as summarized in Table III, we have the distinct impression that such a case is much more likely to achieve such a bacteriological result with the use of INH-PZA, and it seems important to us to direct further statistical evaluation along such comparative lines. Of course, for the patient who has become resistant to SM-PAS and who still needs potent antimicrobial therapy, I think few will disagree that INH-PZA is the most effective available combination.

It should be pointed out that in this study in which we participated as a unit of the Veterans Administration-Armed Forces Cooperative Study of the Chemotherapy of Tuberculosis, the duration of PZA administration extended to as long as 25 months as part of a planned program investigating INH-PZA. With subsequent change in the research protocol of this study, it is now our practice to stop PZA and continue INH alone after four months of combined treatment in those cases in whom cavity closure has occurred; in the persistent open negative cases, we are maintaining INH-PZA for a somewhat longer period. Early experience with these new regimens indicate no loss in therapeutic efficacy as compared with our larger experience of continued combined therapy, and this new program may logically be expected to significantly decrease the substantial number of cases of hepatotoxicity which in our series occurred between the fourth and 10th month of PZA administration.

Acknowledgement: The writer gratefully acknowledges the cooperation of the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey.

SUMMARY

1. One hundred fourteen patients were treated with the combination INH-PZA for periods of one to 25 months.

2. Of eight showing no change on roentgen evaluation at the fourth month of

treatment, it is considered significant that all eight had achieved bacteriological "conversion" and that five of the eight had persistent open cavity with negative sputum. Of 58 moderately and far-advanced cases, 22 showed marked improvement, 17 moderate improvement, 10 slight improvement, and only one showed worsening.

3. Of 55 treated at least four months with moderately and far-advanced disease, 80 per cent achieved bacteriological negativity during the first two months, with the vast majority doing so during the first month of treatment. An additional 13 "converted" during the third and fourth months. Four patients (7 per cent) remained positive, and they all became resistant to INH within two months.

4. Of 19 cases with a cavitary component 4 cm. or more, 11 became "open negative," four became "closed negative," and four remained "open, positive, resistant." Evidence of hepatic toxicity was obtained in 15 per cent of 114 cases only by an abnormal liver function test. Clinical hepatic involvement as well occurred in an additional 4 per cent. There was one death with jaundice; its relationship to PZA is doubtful. All evidence of hepatic toxicity, clinical or laboratory, appeared in a scattered fashion during the first 10 months of treatment; no toxicity was detected in 12 cases receiving PZA for 10-25 months.

5. The achievement of bacteriological negativity with persistence of open large cavity appears to happen much more often with INH-PZA than with various combinations of SM, INH and PAS.

6. The major disadvantage of INH-PZA therapy is the hepatotoxicity of PZA which manifests itself in most of the cases only by abnormal laboratory tests. Because of this it is felt that INH-PZA should be used only in those cases in whom frequent liver function studies can be done, and that further effort should be directed towards finding more sensitive laboratory indices of early PZA toxicity.

RESUMEN

1. Ciento catorce enfermos se trataron con la combinación INH-PZA de uno a 25 meses.

2. De ocho que no mostraron cambio radiológico después del cuarto mes del tratamiento se considera significativo que todos habían logrado "conversión" bacteriológica y que cinco de esos ocho tenían cavidad abierta persistente con esputo negativo. De 58 moderadamente y muy avanzados, 22 mostraron mejoría marcada, 17 moderada mejoría, 10 ligera mejoría y uno empeoró.

3. De 55 tratados por lo menos 4 meses con enfermedad moderada o muy avanzada, 80 por ciento lograron negativación bacteriológica durante los primeros dos meses la mayoría lo lograron de ellos obteniendo tal cambio al fin del primer mes.

Otros 13 se convirtieron durante el tercero y el cuarto meses.

Cuatro enfermos (7 por ciento) permanecieron positivos y todos ellos se hicieron resistentes a la INH dentro de dos meses.

4. De 19 casos que tenían cavidades de 4 cms. o más, once se hicieron "negativos abiertos," cuatro "negativos cerrados" y cuatro permanecieron "positivos abiertos resistentes." Hubo evidencia de toxicidad para el hígado en 15 por ciento de los 114 casos sólo por función hepática anormal según pruebas. También hubo compromiso hepático según la clínica en otro 4 por ciento adicional. Hubo una muerte por ictericia; su relación con la PZA (pirazinamida) es dudosa. Todos las evidencias de toxicidad para el hígado ya fuese clínica o de laboratorio apareció en forma diseminada durante los primeros 10 meses del tratamiento; no se encontró toxicidad en 12 casos que recibieron PZA por 10 a 25 meses.

5. El obtener negativación bacteriológica con persistencia de cavidades abiertas grandes parece que acontece más a menudo con la asociación INH-PZA que varias combinaciones de estreptomicina, isoniacida y PAS.

6. La toxicidad para el hígado por parte de pirazinamida parece ser la desventaja mayor para la asociación INH-PZA la cual se manifiesta sólo en la mayoría de los casos por reacciones de laboratorio anormales.

Por esto se cree que la PZA-INH debe usarse sólo en casos en qiuenes se pueden hacer frecuentes pruebas de función hepática y que se deben hacer esfuerzos para hallar índices de laboratorios más sensibles para descubrir tempranamente la toxicidad de la PZA.

RESUME

1. 114 malades furent traités para l'association isoniazide-PZA pendant des périodes allant d'un à 25 mois.

2. Sur 8 cas ne montrant pas de modification à l'examen radiologique au quatrième mois de traitement, l'auteur considère comme significatif que pour tous on avait obtenu la négativation bactériologique et que cinq cas sur les huit montraient la persistance d'une cavité ouverte avec expectoration négative. Sur 58 cas modérément ou très avancés, 22 montrèrent une amélioration marquée, 17 une amélioration modérée, 10 une légère amélioration et un cas seulement s'aggrava.

3. Sur 55 cas traités pendant au moins quatre mois et atteints de tuberculose modérément ou très avancée, 80% négativèrent leur expectoration pendant les deux premiers mois, la grande majorité d'entre eux pendant le premier mois de traitement.

Treize autres cas négativèrent leur expectoration pendant le troisième et le quatrième mois. Quatre malades (7%) restèrent positifs et devinrent tous résistants à l'isoniazide en moins de deux mois.

4. Sur 19 cas atteints de lésions cavitaires d'une dimension de 4 cm. ou plus, 11 devinrent des "cavitaires avec expectoration négative," quatre transformèrent leurs lésions en cavités fermées avec expectoration négative, et quatre restèrent "cavitaires, positifs et résistants." On n'obtint la preuve de la toxicité hépatique dans 15% des 114 cas que par un test anormal de la fonction hépatique. Une atteinte hépatique clinique survint dans 4% des cas. Il y eut une mort par ictère; son rapport avec le PZA est douteux. Des manifestations de toxicité hépatique, clinique ou bactériologique, apparurent de façon sporadique pendant les premiers dix mois du traitement; on ne put mettre en évidence aucune toxicité sur 12 cas ayant été traités par le PZA pendant 10 à 25 mois.

5. L'apparition de négativation bactériologique avec cependant persistance d'une cavité ouverte volumineuse semble être bien plus fréquente avec l'isoniazide-PZA qu'avec différentes associations de streptomycine, isoniazide et P.A.S.

6. L'inconvénient majeur du traitement par l'isoniazide-PZA est la toxicité hépatique de la PZA qui se manifeste dans la plupart des cas seulement par des tests de laboratoire anormaux. En conséquence, l'auteur pense que l'isoniazide-PZA ne devrait être utilisé que dans les cas où des études fréquentes de la fonction hépatique peuvent être réalisées. On devrait diriger nos efforts ultérieurs pour trouver des épreuves de laboratoire qui indiquent de façon plus sensible les premiers stades de la toxicité de la PZA.

ZUSAMMENFASSUNG

1. 114 Patienten wurden mit der Kombination INH-PZA während Zeiträumen von 1-25 Monaten behandelt.

2. Von 8 Patienten, die bei der röntgenologischen Auswertung im 4. Behandlungsmonat keine Veränderung zeigten, wird als bedeutsam angesehen, dass sämtliche Patienten bakteriologisch eine "Konversion" erreicht hatten und dass 5 von ihnen persistierende offene Cavernen hatten mit negativem Sputum. Von 58 mässig bzw. weit fortgeschrittenen Fällen zeigten 22 eine deutliche Besserung, 17 eine mässige Besserung, 10 eine leichte Besserung, und nur 1 zeigte eine Verschlechterung.

3. Von 55 mindestens 4 Monate mit mässig und mit weit fortgeschrittenen Krankheitsformen behandelten Fällen erreichten 80% bakteriologische Bazillenfreiheit während der ersten 2 Monate, wobei die grössere Zahl dies während der ersten Behandlungsmonate zuwege brachte. Weitere 13 Patienten wurden negativ während des 3. und 4. Monats. 4 Kranke (7%) blieben positiv und wurden gegen INH innerhalb von 2 Monaten resistent.

4. Von 19 Fällen mit Cavernen im Durchmesser von 4 cm oder mehr wurden 11 "offen negativ", 4 wurden "geschlossen negativ" und 4 blieben "offen, positiv, resistent". Beweis für eine Lebertoxizität fand sich bei 15% von 114 Fällen nur durch eine veränderte Leberfunktionsprobe. Klinisch trat eine Leberbeteiligung trotzdem noch in weiteren 4% auf. Ein Todesfall trat ein mit Gelbsucht; seine Beziehung zu PZA ist zweifelhaft. Alle Beweise für die Leber-Toxizität, sei sie klinisch oder im Laboratorium ermittelt, trat in zeitlicher Streuung während der ersten 10 Behandlungsmonate auf; eine Toxizität liess sich nicht ermitteln bei 12 Fällen, die PZA 10-25 Monate lang erhalten hatten.

5. Das Erreichen bakteriologischer Bazillenfreiheit mit Bestehenbleiben grosser offener Cavernen scheint häufiger mit INH-PZA aufzutreten als mit den verschiedenen Kombinationen von Streptomycin, INH und UAS.

6. Der hauptsächliche Nachteil der INH-PZA-Therapie ist die Leber-Toxizität des PZA, die sich in den meisten Fällen nur durch abnorme Laboratoriumsteste manifestiert. Aus diesem Grunde wird die Auffassung vertreten, dass INH-PZA nur in solchen Fällen angewandt werden sollte, bei denen häufige Leberfunktionsproben ausgeführt werden können, und dass weitere Anstrengungen unternommen werden müssen in der Hinsicht, dass stärker empfindliche Laboratoriumsindikatoren gefunden werden zur frühzeitigen Entdeckung der PZA-Toxizität.

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An Historical Outline of Laennec*

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The American College of Chest Physicians has adopted as its emblem the thinking figure of Laennec. By so doing, it pays homage to the savant who permitted the birth of pneumology and it proclaims the action of the genius who made possible the clinical study of diseases of the heart and lungs.

On the occasion of the reunion in Mexico City of a group of distinguished members of the American College of Chest Physicians, I want to offer in their honour, a brief outline of the man who symbolizes their College. I want to show them, in a few strokes, the brilliant work of the most illustrious of their predecessors in the science they cultivate, something like a historic medallion of René Théophile Hyacinthe Laënnec.

When he began his studies in the old Faculty of Medicine of Paris on the 6 Frimario of the IXth year of the Revolution, that is, on the 27th of November of 1801, clinical medicine was only in its beginnings. Despite the 25 centuries elapsed in the midst of oft painful efforts, the clinical study of a patient was something more of an intuition than of an observation; more of a guesswork than a study. The clinical history was lacking sound basis since the symptoms had no correct semiological interpretation. Physical examination was limited to palpation, which rendered meager information and percussion was just starting as advocated by Auenbrugger and Corvisart. It was practised tapping directly on the chest with four fingers, which made it quite imperfect in its beginnings. Yet it was capable of rendering the first positive information such as the concept of fullness and emptiness, the dimensions of the precordial area, the presence of fluid within the pleural cavity and the congestive state of the lung.

Auscultation did not exist. Nobody had made of it an exploratory method until one day of the year 1816, in one blow of brilliant intuition, it was invented by Laennec.

Before his time, surely, there were some who listened to the chest of their patients, and they might even have obtained isolated data. Before him many had, no doubt, listened, but had not learned to listen. That is why Laennec is one of those rare cases in science: that of the discoverer without precursors. Only the old father of medicine, Hippocrates in his book "An Account of the Diseases," speaks of sucusion, which indicates the presence of hydropneumothorax. "You will know by this—he said—that the chest has water and not pus; and applying the ear over the side of the chest, you will hear a noise similar to that of boiling vinegar." This assertion is false, as pointed out by Laennec, but the proof is beyond doubt that Hippocrates evidently used direct auscultation. Hippocrates also

*Presented before the Mexican Chapter, American College of Chest Physicians, Mexico City, January 27, 1959, in commemoration of the Silver Anniversary year of the College.

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heard pleural rub as proved by the following paragraph: "The patient with pleurisy feels as though he had a weight on his chest; he is bothered by acute pains, and he has a noise such as that produced by leather."

For twenty centuries posterity lived making comments on the work of the father of medicine. It is surprising how generation after generation of physicians went by, and no one thought of applying his ear to the chest of his patients. No document is available to prove that any one was curious enough to practise something that seems elementary, almost childish. It was not until the XVIIth century when Grimaldi detected the sound of the contracting muscles, which he attributed to the stirring of the animal spirits which ran back and forth. It was in that same century when Harvey listened to the area of the heart and described a noise similar to that of deglutition of the horse, and he attributed it to the passage of the venous blood into the systemic arterial circuit. This undeniable auscultatory fact, however misinterpreted, gave rise to one of the most shameful controversies in the history of medicine. Aemilius Parisanus objected to the discovery of circulation by Harvey, and went as far as to say that the noise described in the precordial region only existed in the imagination of the British physician, and with an ironic sentence which turns against him because of its poor spirit, he added: "That noise is only heard in London; no doubt we in Venice are deaf." Yes, he belonged to those doomed to condemnation by the Biblical sentence among whom "having ears will not hear."

In the following two centuries there were scarcely two shy attempts, that of Ambroise Paré, who described a noise similar to that of a half-full bottle which bubbles, in patients who have a humour contained within the chest. And Bayle's, in the beginning of the XIXth century, a classmate of Laennec, who used to apply his ear to the chest of his patients, without obtaining any more information, according to Laennec himself, than that of "feeling with greater force the beats of the heart in cases wherein the hand does not distinguish them clearly."

Such was the state of exploratory methods of diseases of the heart and the chest in the early part of the XIXth century. A desolate panorama which corresponds to the poverty of medical knowledge of that period, when the only solid foundations of future medicine were the beautiful studies of human anatomy of Andrea Vesalius; the physiological demonstration of the circulation of the blood by Harvey; the patient clinical-pathological confrontations, made first in the Italian School by Lancisi and Morgagni, and afterwards by Sénac and Corvisart of the French School. And finally, the extraordinary intuition of the great precursors of the clinical method, scattered in different countries, who attempted to discover the truth. They were stopped by a solid wall which prevented them from coming close to the diagnosis of pathology of the heart and the lungs. They had no trustworthy exploratory methods. Thence the bitter discouraging reflection of Baglivi: "O quantum difficile est curare morbus pulmonum! O quantum difficilius eosdem cognoscere!"

This is when Laennec made his appearance. Forgotten in the dust of oblivion the two observations of Hippocrates and fruitless up to that time the attempt of Bayle, one cannot say that auscultation was in existence as an exploratory method. It was born the day it was invented by Laennec.

It is well known, because he told it himself, how the idea came to his mind; how one day, recalling the acoustic phenomenon on the fact that "if the ear is applied to the extremity of a piece of wood, a simple scratch produced in the other end is clearly heard"; he made a tightly-rolled paper tube, he applied one of its ends to the precordial area and applied his ear at the other end. "My surprise—he wrote—was only equalled by my satisfaction when I heard the cardiac beats more clearly and distinctly than I had ever heard them with the direct application of my ear." And he added: "I thought at once that this means could become a useful method, applicable not only to the study of the heart beat but also to that of all the movements which may produce a noise within the chest cavity. With this conviction, I immediately began a series of observations at the Necker Hospital, which has given me new, positive, easy to detect signs useful for the diagnosis of almost all the diseases of the lungs, the pleurae and the heart, something more certain and circumstantial, perhaps, than the diagnoses made with the aid of a sound or the introduction of a finger."

This was one of the most wise, patient and fruitful investigations of which the human intellect can be proud. In his unwaning desire for perfection, Laennec modified one hundred times his device until he found the adequate conditions for the best results. The primitive paper tube was followed by glass, metal and baudruche devices; he made them light, heavy, sometimes solid, sometimes perforated; first long, then short; made of one piece and afterwards of several pieces, until finally he adopted a wooden cylinder of moderate density, made of two portions widened at their ends and perforated in the middle, in order to allow their transformation into a thick-walled tube by the simple application of an obturating piece. To this instrument he gave the name of stethoscope. With this stethoscope the entire pleural and lung pathology was created.

Three years were enough time for Laennec to edit his work *"De l'auscultation médiate,"* which appeared in 1819. To it were added seven others for the preparation of the final edition of his treatise. Ten years in all, bent over the beds of his patients, with the stethoscope in his hand, or else over the autopsy table, confronting the signs with the anatomical lesions; ten years sufficed to conceive, develop and perfect his work. Ten years of exhausting work which sufficed for him also, to take sick with tuberculosis which led him to his grave on the 13th of August of 1826.

It is useless to recall here, among learned specialists, the extent and depth of the work of Laennec. To evalue it, suffice it to say, that before him there was nothing. One could imagine, for that purpose, a traveller who penetrates an unexplored jungle where each species was unknown and where each plant, each tree and each flower were of a type and structure never before imagined. Such was the case with Laennec when he heard the sounds for the first time. As Cuvier did in his investigations on the animal kingdom, he had to begin by giving names and classifying one by one the phenomena he discovered. Thereafter he had to find an explanation for them. Admirable pathologist that he was, he confronted always the signs detected in life with the lesions found at autopsy. Hence the fact that his descriptions and his interpretations have resisted almost invariably the passage of time and that they continue to be true in our day.

I will not delve into his findings, but will limit myself to enumerate the principal ones. He described the breath sounds of the lung with all their physiological variants or with all the pathological variants such as the bronchial respiration and cavernous respiration. He studied the transmission of the voice and he described with precision bronchophony, pectoriloquy and egophony. He established the intimal relationship which the egophony has with the presence of fluid in the pleural cavity. He devised the indispensable proof and counterproof and when he reached a verdict he was so irrevocably certain that he proudly said: "I believe it would be very difficult to determine with greater accuracy the relationship between the bronchi and pleural effusion producing egophony." In the medical profession of that time these words were received with astonishment and skepticism. Broussais made a sarcastic comment: "Mr. Laennec maintains all of this with the most daring audacity . . . It would seem that he has introduced himself within the chest of his patients."

He studied the modifications heard during cough and the different types of rales. He described them all and gave the explanation for their production and the diseases causing them.

He auscultated the heart and gave us significant basic facts. He described the two cardiac sounds; he discovered murmurs; he pointed out for the first time the double murmur of the basal area in aortic valve disease and he described the pericardial rub. Laennec was never primarily concerned with the heart. It was the lung which attracted all his attention. Heart physiology was in those days very rudimentary. It is conceivable that in this field his physiologic interpretations were sometimes erroneous. He believed that the two sounds of the heart were due to the contraction of the auricles and the contraction of the ventricles for the first and second sound respectively. Murmurs he invariably interpreted as due to valvular lesions; yet, in the second edition of his treaty he corrects himself. Observing that sometimes autopsy did not disclose a valvular damage, and in view of the fact that the murmur was heard in cases with severe anemia, of extreme exhaustion or nervous conditions, he changed his original views and denied any importance to valvular lesions. Such was the honesty of an investigator who errs once again but without fear of correcting himself.

Laennec went beyond the pure finding of physical signs and anatomical lesions and he then gives proof of his profound insight. With the material derived from his anatomical confrontations, he built the unitarian doctrine of tuberculosis and he identified the tubercle with the cavern. He founded also the method for the study which was to be applied to all the diseases in order to change mere speculations for positive facts. He proclaims himself against hypothesis without basis which he regards as mere fiction. He shook the old medical edifice and destroyed the systems used for centuries. Laennec represented the advent of a new era. His projection in medical history is like that of a new Hippocrates, a Hippocrates of our time.

His work was not always accepted; indeed, the past defended itself furiously and attacked him relentlessly. There was also some praise, but there was more censorship, bitter, disrespectful and hurting, pro-

pounded by a group. Meanwhile the great mass of physicians remained deaf, with a dumb smile of incredulity on their lips. Laennec fervently defended his ideas and gave proof of his stature as a formidable polemist. To those denying the usefulness of auscultation, objecting that they were unable to hear anything or stating that the signs described were fallacious, he replied: "If any physician who has never seriously applied himself to surgery decides at the age of 40 years to practise cutting of the stone without training and without the advice of an accredited surgeon, it could very well happen that he operated on patients without stones; that he does not find the stone when it is there or that he may be unable to introduce a catheter in the bladder, especially if he operates with the desire to find something impracticable, as seems to be the case with the majority of those observers. Furthermore, there are also deaf people and the worst deaf are those who do not wish to hear."

Broussais rose in great anger and spoke in the name of pathologic physiology and formulated execrations against this innovator. The nature of the charges portrays the ideology of the time: "Pathologic alterations, considered in themselves—said Broussais—are mere curiosities and lack any interest for he who studies them, since inflammation is the cause of these alterations; but even if one other should be the cause, we should only concern ourselves with pathologic physiology." The lesions of emphysema, those of melanosis, the tubercles themselves, all which Laennec had described, were useless in the opinion of Broussais. "What the physician must know—he added—is that everything that Mr. Laennec has said concerning his black cancers is purely imaginative and is none other but an obscure account of something which is very hard for me to read." "I do not know—replied Laennec—if my work is lengthy or hard to learn. I only know that my black cancers are bodies whose dimensions, consistency and other physical characteristics may be comprehended by the senses; while the inflammation referred to by Mr. Broussais, which he defines as the exultation of the vital properties, is nothing but an imagined figure, a hypothesis which is very unlikely in the majority of the cases."

Irritating to Broussais and his partisans was the minute description of the lesions, which forced them to abandon the reading. Irritating also was the difficulty to retain the facts, because of the multiplicity of lesions which were almost always present in the autopsy. "True—said Laennec—but I have neither intended to write a recreative paper nor did I intend for my findings to be memorized; much less will I ever leave out anything that I find."

The proud certainty of Laennec when he categorically maintained his ideas concerning the evolution of the tubercles won him the sarcastic nickname of a guesser. "Mr. Laennec makes his statements with an admirable audacity—reproached Broussais—It would seem that he might have been inside the body of his patients at the very moment when matter was under the crude state and thereafter he saw it grow and invade the tissues." "But does Mr. Broussais imagine—replied Laennec—that the naturalist who finds the larvae in the brush, the nymph and the butterfly in its different stages of development must need, in order to describe the metamorphosis of the insect, to enclose himself within the egg or within the cocoon? Does Mr. Broussais believe that perhaps Bunter, Meckel, Tiller-

man and Pander have introduced themselves within a mother in order to study the development of the fetus?"

The case of Laennec is the most extraordinary instance of the paradox within the logic of investigation. When he was a student in the clinic of Corvisart he repeatedly observed Bayle and other classmates practise direct auscultation and he himself practised it often. Yet he never found it useful. Phenomena did not clarify themselves nor did they clarify his own mind. "It merely serves—he said—to hear with greater force the sound of the heart." But once he invented the stethoscope, the primitive paper stethoscope, Laennec saw how the horizon stretched indefinitely. As with Paul on his way to Damascus, his thought was suddenly enlightened, and with his primitive and imperfect cylinder, he found everything that was to be found. He trusted the virtue of his device with the unbinding faith of a believer and he used it for everything, even to percuss. To it he attributed his success. It was his fetish. Without the stethoscope, Laennec might have continued perhaps to apply his ear to the chest of his patients without finding anything, as had happened during the several previous years.

This heuristic virtue of the stethoscope is the same one which permitted Piorry, some years later, with the invention of his plesymeter, to modify the old direct percussion and derive all the benefit of percussion possible. Laennec, without his stethoscope and Piorry without his plesymeter, great fetishes of these two investigators, might not have found anything. Heuristic virtue, somewhat difficult to understand, wherein are united the obsession of the savant who found his way with the pride of the inventor, who is determined to make out of his invention, the magic clue of truth.

I have tried to outline to you a fraction of human thought, the work of a man who was a genius and the struggle of an arising era against another one, old and decadent. The era of pathologic anatomy, of physical signs, of positive findings, against the era of empyrical knowledge, of aprioristic doctrines, of the hypothesis without sound base. Humanity in its progress often changes its route. The scientific criterion of our day does not seek, as Laennec did, the explanation of morbid phenomena from exclusive or even preferent study of the lesions. Today it seeks in the physiological and biochemical processes. The new men follow this path, but they are forced to know of this milestone of the medical thought, because in it is contained a good portion of the truth we possess. If we wish to know, we must not start out by ignoring. And if the old truth does not suffice, it is well to seek other paths without forgetting, however, the advice of Laennec himself: "Whenever phenomena are uncertain, one must rely on positive facts and from them we may introduce ourselves cautiously into the realms of doubt."

Allergic and Toxic Reactions of Prolonged Chemotherapy for Pulmonary Tuberculosis

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It has been about 10 years since the introduction of streptomycin in the treatment of pulmonary tuberculosis. Since that time, paraminosalicylic acid (PAS) and Isoniazid (INH) have been added to the armamentarium of treatment. Many new drugs are now being studied with research being done to improve their therapeutic effectiveness, in addition to reducing their side effects, as a result of prolonged use.

We are concerned, in this report, with the side effects produced by these drugs. This study was originally undertaken to determine whether reactions which had not occurred early in the treatment, were likely to occur after prolonged use of these drugs. Streptomycin, INH, and PAS were the only drugs studied.

The difference of opinion which exists regarding how long antimicrobial therapy should be given is not a new one. You are aware of this controversy, as in our own Committee on Tuberculosis of the Texas Medical Association. In a recent article by the Committee, a summary was made for setting a standard of treatment. Since we are interested in pointing out the allergic and toxic reactions of prolonged administration, it is important to us to know what the opinion is regarding prolonged treatment. A statement was made that "If, after approximately 18 months on drugs, the patient is apparently well, his roentgenograms show a healed or healing lesion, and his sputum cultures are consistently negative for mycobacterium tuberculosis, then the doctor should consider stopping drug therapy." If the prolonged use of drugs produces toxic and allergic manifestations, then this fact should be given consideration, not only in the treatment, but also in the choice of drugs. Reactions were studied to determine how long after the onset of treatment they developed, and the significant differences in the type and severity of early and late reactions.

Clinical Material

The patients were seen on routine follow-up examinations varying from one to four months. Then, they were examined, a 14 x 17 roentgenogram was taken, sputum studies for smear and culture were made, urinalysis and cephalin flocculation tests were done. A complete blood count was routine. The patients were seen at the City of San Antonio Public Health Chest Clinic. All of them were ambulatory, many received injections and medications at this installation or neighborhood clinics prior to entering the hospital. The study was made during the years 1954, 1955, and 1956. The total number of patients under treatment during any one year was 8,122, of which 5,033 were old and 3,089 were classified as new cases. The total number of streptomycin injections given during this one year,

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1955-56, was 20,144. The total clinic visits during this period was 40,884. In the group studied, there were nine pregnant women who came under our observation. They were active or inactive cases who during the course of their treatment became pregnant. The patients were predominantly of Latin-American extraction.

Case Reports

Case 1. Otic Type (Deafness): A 33 year old Latin-American woman first had a diagnosis of pulmonary tuberculosis, far advanced, active, at the City Chest Clinic. She was started on streptomycin and PAS on admission to the McKnight Sanatorium on October 20, 1951. She was discharged on June 30, 1954, using streptomycin and PAS. On August 25, 1954, PAS was discontinued and INH was started. On September 9, 1954, she developed marked itching of the eyelids, complained of impaired vision, following which she developed generalized erythematous rash. She had complained of mild hearing impairment during the past 5 years. This had become progressive, especially in the right ear. On March 1, 1955, audiometric examinations revealed considerable hearing defect bilaterally, more on the right side. She was placed on PAS and INH and the hearing of the left ear improved. In December 1955, there was a spread of the tuberculosis in both lungs and the patient was admitted to the San Antonio State Tuberculosis Hospital on January 26, 1956. PAS and INH were continued until medical discharge on November 26, 1956. On discharge she had pulmonary tuberculosis, far advanced, inactive, and deafness.

Case 2. Allergic Type (Anaphylactoid Reaction): A 53 year old Latin-American was first diagnosed pulmonary tuberculosis, far advanced, active, on May 30, 1952, at the San Antonio City Health Department Chest Clinic. He was started on Streptomycin and PAS on June 23, 1952, and was hospitalized at the McKnight Sanatorium from June 20, 1953 until October 23, 1954. He continued on streptomycin and INH and extrapleural pneumonectomy was performed. After discharge on October 23, 1954, he was followed at the City Chest Clinic and received streptomycin and INH. On March 17, 1955, immediately following a usual streptomycin injection, he became agitated and complained of nausea. A short time later, he became weak, complained of vertigo and needed support. This was followed by a mild convulsive seizure and complete unconsciousness. Treatment for shock was instituted and he responded well with resulting weakness. Streptomycin was discontinued and PAS and INH used until June 7, 1957, when he refused further treatment because of continued weakness.

Case 3. Neurologic Type (Peripheral Neuritis): A 22 year old Latin-American woman was first found to have pulmonary tuberculosis at the City Chest Clinic on September 8, 1950. She had started on streptomycin and INH on April 22, 1954. On January 27, 1956, approximately 20 months after she had started on antimicrobial therapy, she complained of numbness of the face after each injection. She was reexamined but had no abnormal findings. Since this was a common complaint in people receiving treatment, no particular recommendation was made. Two months later, she developed muscle cramps and aching in both legs which became quite severe. She was found to be pregnant. She was given pyridoxine and thiamene daily. On March 30, 1956, following her regular streptomycin injection, she developed a typical severe allergic urticarial rash on the entire body. She complained of more severe pain in the lower extremities with impairment of muscle strength. There was some evidence of hyperesthesia on examination of the legs. Streptomycin was discontinued and PAS and INH started. On October 15, 1956, she delivered a full-term infant with no complication. On September 9, 1957, she was again started on streptomycin and INH when her sputum became positive for acid fast bacilli. She has had no further dermatologic manifestations.

Case 4. Hematologic (Granulocytopenia): A 34 year old Latin-American was first diagnosed as having pulmonary tuberculosis, moderately advanced, active, at the City Chest Clinic on December 13, 1952. He was started on streptomycin and PAS on March 3, 1953. A complete blood count was done at that time and found to be normal. As treatment with anti-microbial drugs progressed, there was a gradual reduction in total white blood count. He was being prepared for surgery, so anti-microbial therapy was continued. On April 1, 1954, because he complained of marked vertigo and numbness about the mouth, streptomycin was discontinued and PAS and INH instituted. In spite of the discontinuation of the streptomycin, the white blood count became further depressed and remained between 2900 and 4900. On December 18, 1956, he complained of marked weakness and tiredness. The white blood count was 2900 and the hemoglobin was 75 per cent. He was given vitamins, antibiotics, and anti-tuberculosis therapy was discontinued.

Case 5. Hematologic (Granulocytopenia): A 59 year old Latin-American was found to have pulmonary tuberculosis, far advanced, active, and diabetes mellitus on February 16, 1949. On June 3, 1951, he was started on streptomycin twice a week and PAS daily.

This treatment was continued until July 26, 1951, when it was discontinued because of leukopenia and relative agranulocytosis. The white blood count was 3400. The red blood count was 3,600,000 and the hemoglobin was 70 per cent. Penicillin was started and was given until August 14, 1952. Streptomycin with PAS, was again started and weekly complete blood counts were reported. He again was able to receive the treatment for a period of nine months. On September 11, 1952, he refused treatment because of marked vertigo, nausea, vomiting, and diarrhea. He was followed at the City Chest Clinic from October 14, 1953, to the present time. He had granulocytopenia due to drug reaction. Present blood counts have been normal and his disease has been classified as pulmonary tuberculosis, far advanced, inactive, and diabetes mellitus, controlled.

Case 6. Hepatic (Jaundice): A 57 year old white man had a diagnosis of pulmonary tuberculosis, moderately advanced, active, on December 14, 1954. He was started on the usual dosage of streptomycin and INH. He was admitted to the sanatorium one month later, where he began to have hematuria and oliguria. Sputum and urine cultures were negative for acid fast bacilli. He left the hospital against medical advice just after he had developed slight anemia and jaundice. The red blood count was 2,610,000, hemoglobin of 51 per cent, and white blood count of 7300. On July 14, 1955, while he was receiving streptomycin and INH at the City Chest Clinic, he developed clinical jaundice with anemia. He was admitted to the Robert B. Green Memorial Hospital after the anti-microbial drugs had been changed to streptomycin and PAS. On examination, the liver was found to be enlarged and tender. He was observed in the hospital for approximately three weeks. Surgical consultation was held and because of localized pain in the right upper quadrant, cholecystectomy was done. Stones were not found and he made an uneventful recovery. He received streptomycin and PAS during the entire hospitalization. One year after surgery, he was still receiving antituberculosis therapy and had no more hepatitis. His red blood count, however, remained depressed to 3,200,000, hemoglobin 59 per cent, and white blood count 5500.

TABLE I
CLASSIFICATION AND INCIDENCE OF 100 ALLERGIC AND TOXIC REACTIONS

Type	Total Number of Cases	Number of Cases of Each Type
I. OTIC	29	
A. Deafness		17
B. Vertigo		12
II. ALLERGIC	17	
A. Urticarial		10
B. Angioedema		4
C. Anaphylactoid		3
III. CEPHALGIA	14	
A. Headache		14
IV. GASTRO-ENTEROLOGIC	11	
A. Gastro-intestinal upset		11
V. NEUROLOGIC	11	
A. Peripheral Neuritis		9
B. Nervousness & Insomnia		2
VI. DERMATOLOGIC	8	
A. Eczematous Reaction		7
B. Pityriasis Rosea		1
VII. HEMATOLOGIC	5	
A. Anemia, severe		3
B. Granulocytopenia		2
VIII. ARTHRITIC	4	
A. Rheumatoid		4
IX. HEPATIC	1	
A. Jaundice		1
Total	100	

Findings

Table I shows the classification and incidence of allergic and toxic reactions in 100 cases. It was found that there were many mild and transient reactions which could not be classified. All reactions were classified as otic (29), allergic (17), cephalgia (14), gastro-enterologic (11), neurologic (11), dermatologic (8), hematologic (5), arthritic (4), and hepatic (1). The number of cases in each classification is given and the most frequently occurring reactions were related to the ear. Each group was further subdivided to better characterize the reactions.

Table II shows the time elapsed from the first use of the drugs to the first appearance or reaction. It is noted that the greatest number of reactions occurred in the first six months, 33. There was a total of 49 reactions in the first 12 months, 68 reactions in the first 18 months, and 82 in the first 24 months. The total number of reactions after 24 months was only 18. These findings point out that reactions to these drugs are not an important consideration in prolonged therapy, since the greatest percentage of reactions occurs early in therapy. The severity of the reac-

TABLE II
LENGTH OF TIME ELAPSED AFTER FIRST USE OF DRUGS TO FIRST APPEARANCE OF REACTIONS

Type of Reaction	Total cases	6 months	12 months	18 months	24 months	30 months	36 months	40 months
I. OTIC								
A. Deafness	17	4	2	6	1	1	2	1
B. Vertigo	12	7	2	2	0	0	0	0
II. ALLERGIC								
A. Urticarial	10	0	0	3	3	3	1	0
B. Angioedema	4	2	2	0	0	0	0	0
C. Anaphylactoid	3	0	1	0	1	1	0	0
III. CEPHALGIA								
A. Headache	14	5	1	3	2	1	0	2
IV. GASTRO-ENTEROLOGIC								
A. G. I. Upset	11	5	5	1	0	0	0	0
V. NEUROLOGIC								
A. Peripheral Neuritis	9	2	1	1	4	1	0	0
B. Nervousness-Insomnia	2	2	0	0	0	0	0	0
VI. DERMATOLOGIC								
A. Eczematoid	7	4	2	1	0	0	0	0
B. Pityriasis Rosea	1	0	0	0	0	1	0	0
VII. HEMATOLOGIC								
A. Anemia, Severe	3	0	0	2	0	1	0	0
B. Granulocytopenia	2	1	0	0	1	0	0	0
VIII. ARTHRITIC								
A. Rheumatoid	4	0	0	0	1	0	1	2
IX. HEPATIC								
A. Jaundice	1	1	0	0	0	0	0	0
Totals	100	33	16	19	14	9	4	5
Total Before 24 Months	82							
Total After 24 Months	18							

tions appears to be greater in the first year of treatment. It is seen that reactions can, however, occur as late as 40 months after the onset of treatment.

Eighty-three cases were using streptomycin and INH at the time of reactions. Fourteen were using streptomycin and PAS and only three were using PAS and INH. Changing the drugs to PAS and INH would improve the situation and allow for uninterrupted treatment. Many of the allergic cases needed antihistamines and steroids as additional treatment. The eventual outcome showed improvement in all except four cases. In these, the treatment had to be discontinued.

A study of the reactions and results of drug therapy in the pregnant patients is given. We had no inactive or arrested patients reactivate. The anemias which resulted seemed to continue after pregnancy. No untoward effects were noted in the mother or the fetus. We feel that pregnancy is not a valid reason for interrupting treatment, even though reactions do occur. In this group, the most frequently occurring reaction was hematologic, exemplified by severe anemia. Neurologic was next.

COMMENT

The use of multiple drugs in therapy over long periods of time make it almost impossible to prove sensitivity to any one of them. The frequency of otic and allergic reactions tends to incriminate streptomycin. As seen in Table II, most of the reactions occurred while these patients were using streptomycin and isoniazid. Most of the reactions appeared in the first 24 months of treatment. The discontinuation of streptomycin gave relief from the reaction in most of the cases. Only four cases needed to discontinue treatment entirely. Fewer reactions occurred with PAS and INH indicating the need for a drug to replace streptomycin. Reactions of all types, both mild and severe, have been reported for INH and PAS. Psychoses, peripheral neuritis, and optic neuritis have been attributed to INH. Goiter with myxedema and peripheral neuritis reported for PAS. In our series, all types of reactions were encountered with streptomycin with the possible exception of exfoliative dermatitis.

This study shows that reactions occur more frequently than is generally appreciated. Documentation of these reactions is seldom investigated. As in this series, the usual procedure is to discontinue the suspicious drug and start a new one.

The reactions seen in pregnancy show no deliterious effects on the mother of fetus. Hematologic reactions, such as severe anemia, had to be followed and treated after delivery.

It is evident from this report that the continued use of multiple drugs, especially streptomycin, should not make us complacent about the future possibilities of toxicity and sensitivity developing. We are of the belief that all these reactions could be classified as hypersensitivity, but proof of this belief is beyond the scope of this report.

Prevention of adverse effects of these drugs by the use of vitamin B, pyridoxine, antihistamines, epinephrine, and steroids should be familiar to those who prescribe them. Hyposensitization of allergy due to these drugs using the oral and injectable steroids is the best method of insuring continuation of anti-microbial therapy. This is especially true in bronchial asthma. Since interruption of therapy alters the course of the disease, it is one's duty to know these facts, especially when using drugs over a prolonged period of time.

SUMMARY

1. One hundred cases of allergic and toxic reactions of multiple drug therapy were studied over a prolonged period of time.

2. The prolonged use of drugs demonstrated that most of the reactions occurred while patients were using streptomycin and isoniazid.

3. The most frequently occurring reactions were in the first 24 months of treatment, and otic and allergic types of reactions were the most common.

4. Pregnancy is not a valid reason for interrupting treatment even though allergic and toxic reactions do occur. Prophylactic treatment of anemia is necessary while using multiple drugs over prolonged periods.

5. Prevention of the adverse effects of streptomycin, izoniazid and paraminosalicylic acid by the use of vitamins, pyridoxine, antihistamines, adrenergic and steroid drugs, should be instituted as soon as the reactions are diagnosed.

6. The most successful prophylactic measure is still the temporary or permanent discontinuation of the offending drugs and the substitution of a better drug, without interrupting therapy.

RESUMEN

1. Se estudiaron cien casos de reacciones alérgicas y tóxicas a drogas múltiples durante largo tiempo.

2. El uso prolongado de drogas demostró que la mayoría de las reacciones ocurrieron mientras los enfermos estaban usando estreptomicina e isoniacida.

3. Las reacciones más frecuentes se presentaron en los primeros 24 meses del tratamiento y fueron las óticas y las alérgicas las más comunes.

4. El embarazo no justifica la interrupción del tratamiento aunque ocurran reacciones tóxicas y alérgicas. Es necesario el tratamiento profiláctico de la anemia mientras se usan drogas múltiples por largo tiempo.

5. La prevención del os efectos adversos de la estreptomicina, isoniacida y PAS por el uso de vitaminas, piridoxina, antihistamínicos y drogas adrenérgicas y esteroides, debe intituirse tan pronto como las reacciones se diagnostiquen.

6. La medida profiláctica más eficaz, es aúm la interrupción temporal o permanente de la droga responsable y la substitución por una droga mejor sin interrupción del tratamiento.

RESUME

1. Cent cas de réactions allergiques et toxiques produites par de nombreuses médications ont été étudiès pendant une période prolongée.

2. L'utilisation prolongée de médications démontra que la plupart des réactions survenaient pendant que les malades utilisaient la streptomycine et l'isoniazide.

3. Les réactions apparurent le plus souvent dans les premiers 24 mois de traitement, et les plus communes furent celles qui touchaient l'oreille ou qui prenaient les caractéres de l'allergie.

4. La grossesse n'est pas une raison valable d'interrompre le traitement même si des réactions allergiques ou toxipues survenaient. Le traitement prophylactique de l'anémie est nécessaire lorsqu'on utilise des médications nombreuses pendant des périodes prolongées.

5. La prévention des effets toxiques de la streptomycine, de l'isoniazide et du P.A.S., par l'utilisation de vitamine, de pyridoxine, d'antihistaminiques et de mèdications hormonales et adrénergiques, devrait être instituôe aussitét que les réactions sont diagnostiquées.

6. Le moyen prophylactique le plus satisfaisant est encore la suspension temporaire ou permanente des médications offensantes et la substitution d'un produit meilleur, sans interrompre le traitement.

ZUSAMMENFASSUNG

1. Es wurden 100 Fälle von allergischen und toxischem Reaktionen auf multiple medikamentöse Behandlung über eine besonders lange Zeitspanne beobachtet.

2. Die verlängerte Verwendung von Medikamenten bewies, dass die meisten Reaktionen auftraten, während die Patienten Streptomycin und INH benutzten.

3. Die am häufigsten vorkommenden Reaktionen waren in den ersten 24 Behandlungsmonaten zu verzeichnen und otologische und alergische Reaktionsformen waren die häufigsten.

4. Eine Schwangerschaft ist kein gültiger Grund zur Unterbrechung der Behandlung, selbst wenn sich allergische und toxische Reaktionen einstellen. Eine prophylaktische Behandlung von Anaemie ist notwendig, wenn man eine multiple medikamentöse Therapie während besonders langer Zeitspannen gebraucht.

5. Eine Verhinderung der ungünstigen Wirkungen von Streptomycin, INH und PAS durch den Gebrauch von Vitaminen, Pyridoxien, Antihistaminica, adrenergischen Medikamenten und Streoiden muss in Gang gesetzt werden, sobald die Reaktionen diagnostiziert werden.

6. Die wirksamste prophylaktische Massnahme ist noch immer die temporäre oder permamente Unterbrechung der schuldigen Medikamente und ihre Ersetzung durch ein besseres Medikament ohne Unterbrechung der Therapie.

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Pyridoxine and the Isoniazid-Induced Neuropathy*, **

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Soon after isoniazid was employed in the treatment of tuberculosis, several investigators noted the occurrence of peripheral neuropathy in adult patients treated with the drug.[1-4] This neuropathy was characterized by symmetrical numbness and tingling of the extremities in the "stocking-glove" distribution. It tended to develop earlier and was more severe in the feet than in the hands. In the early stages sensory manifestations predominated. Later stages were characterized by paresthesia, pain and aching in muscle and bone, hypesthesia, hyperesthesia, diminution of vibratory and position sense, exaggerated or reduced tendon reflexes, ataxia, muscle weakness and muscle paralysis. The neuropathy occurred sooner and was more severe in patients who received a larger amount than the usual isoniazid dose. It tended to regress when isoniazid was stopped, although the longer symptoms were present, the longer it took for them to disappear. In occasional instances the neuropathy was relieved by nicotinic acid, but it was unaffected by thiamin or vitamin B_{12}. A pellegra-like state resulting from isoniazid has been reported[5, 6] but the clinical picture of nicotinic acid deficiency does not resemble the isoniazid-induced neurotoxicity nor does the latter usually respond to the administration of nicotinic acid.

With the commonly employed dose of 300 mg. of isoniazid daily the neuropathy occurs in approximately 2 per cent of patients.[7] Biehl and Skavlem[1] reviewed the incidence of neurotoxicity in 100 patients receiving isoniazid in daily doses of 400 mg. to 1600 mg. Of 65 patients who had not taken isoniazid previously, 11 (17 per cent) developed symptoms or signs of neurotoxicity 24 to 71 days after starting the drug. The remaining 35 patients had received isoniazid immediately previous to the increase in dose and 12 ((33 per cent) developed neurotoxicity as early as six days after this was done. In another study in which 16 patients received isoniazid in amounts ranging from 1100 mg. to 2400 mg. daily, 5 (37 per cent) showed some evidence of peripheral neuropathy. The 30 to 40 per cent incidence of neurotoxicity with high doses of isoniazid was confirmed in a report on the treatment of 116 adult patients.[8]

Although a deficiency of the vitamin B complex had been suggested as the cause of neuropathy, Biehl and Vilter[7, 9] were among the first to relate this to a deficiency in biologically active pyridoxine. These authors measured the 24 hour urinary excretion of pyridoxine and nicotinic acid before, during and after varying dosages of isoniazid. In addition, they determined the amount of xanthurenic acid excreted after a test dose of tryptophane, an increase being evidence of pyridoxine deficiency. They found that the level of pyridoxine increased while the excretion of nico-

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**Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

tinic acid remained unchanged during isoniazid therapy. Twice the normal amount of pyridoxine was excreted when the daily isoniazid dose was 300 mg. and four to five times the normal amount was excreted when the daily dose was 1400 mg. The excretion of pyridoxine promptly returned to normal when isoniazid was stopped. A progressive increase in the excretion of xanthurenic acid occurred following the test dose of tryptophane in some but not in all patients receiving isoniazid. This was reversed when pyridoxine was given. The authors surmised that isoniazid was not a metabolic antagonist of pyridoxine but that it combined with it to form a hydrazone that was excreted in the urine. The hydrazone was considered to result from a chemical reaction between the aldehyde group of pyridoxal 5-phosphate, the active form of pyridoxine, and the free amine group of isoniazid. A subsequent study by Wiegand[10] confirmed the occurrence of this chemical reaction.

Prior to the work establishing pyridoxine deficiency as the cause of the isoniazid-induced neuropathy, Yoneda and associates[11, 12] noted an antagonism between isoniazid and pyridoxine. They showed that isoniazid inhibited indole formation and amino acid decarboxylation by E. coli and that pyridoxine reversed this inhibition. They were thus the first to observe the inhibitory effect of isoniazid on a pyridoxine-dependent enzyme system. Isoniazid, when given in sufficient dosage to appropriate test subjects, is probably capable of inhibiting most enzymatic reactions dependent on pyridoxine and its effects can be counteracted by the administration of pyridoxine.[13]

One other observation suggested the likelihood that the isoniazid-induced neuropathy resulted from a pyridoxine deficiency. This was the study by Reilly and associates[14] on the convulsant effects of unsubstituted hydrazides, isoniazid being one example. Semicarbazide, another example, produced grand mal seizures which could be readily reversed by the administration of pyridoxine. These authors were also aware that patients with both tuberculosis and epilepsy required higher than the normal maintenance doses of anticonvulsant medication when receiving isoniazid.

Peripheral neuropathy is not a serious problem in patients treated with the 300 mg. isoniazid, the commonly employed daily dose. This dose, however, is not sufficient for all tuberculosis patients. One reason for this is that isoniazid is metabolized and altered to derivatives which have little or no antituberculous activity.[15, 16] The rate of this alteration while constant for any one person varies from one individual to another;[15, 17] the same dose of isoniazid, therefore, produces different effective antimicrobial levels of the drug in different persons. For this reason, doses greater than 300 mg. daily have been recommended for all tuberculous patients.[18] Such doses will result in a higher incidence of peripheral neuropathy if pyridoxine is not given concomitantly.

Biehl and associates found that the daily administration of from 50 to 450 mg. of pyridoxine in conjunction with 1400 mg. of isoniazid effectively prevented the occurrence of peripheral neuropathy.[7, 9] In their series, no patient given the two drugs developed peripheral neuropathy within ten weeks, whereas the expected incidence would have been 40 per cent. The

prophylactic value of pyridoxine in preventing the isoniazid-induced neuropathy has been confirmed by two other studies.[19, 20] In one of these,[19] 25 mg. of pyridoxine with a daily dose of isoniazid of 500 mg. to 600 mg. and 50 mg. with a daily dose of 1100 mg. to 1200 mg. effectively prevented the occurrence of peripheral neuropathy. In the other study,[20] the daily administration of 100 to 300 mg. of pyridoxine prevented the occurrence of peripheral neuropathy in patients receiving isoniazid in doses of 1000 mg. to 1800 mg. Pyridoxine was effective in some instances in which the neuropathy had already been established. When pyridoxine was given, it was not necessary to interrupt isoniazid therapy in some patients and, in others, it could be resumed at an early date.

The exact dose of pyridoxine needed to prevent the isoniazid-induced neuropathy has not been established but 10 mg. for each 100 mg. of isoniazid appears adequate. This amount should also be sufficient to prevent any possible or potential subclinical deficiency of this vitamin. The prophylactic use of pyridoxine concomitantly with isoniazid does not interfere with its antituberculous action. Several authors have shown in both animal and human studies that the neurotoxic and antituberculous effects of isoniazid are indepenedent of each other.[21-23]

The complete relationship between isoniazid and pyridoxine is, as yet, not known. One problem is whether isoniazid produces pyridoxine deficiency in children. Employing a relatively insensitive test of pyridoxine deficiency, Morales and Lincoln[24] found that pyridoxine deficiency did not occur in tuberculous children treated with isoniazid and stated that prophylaxis with pyridoxine was not required.

SUMMARY

The isoniazid-induced peripheral neuropathy occurring in adult tuberculous patients results from a deficiency of biologically active pyridoxine. The deficiency is caused by the combination of isoniazid and pyridoxine to form a hydrazone which is excreted in the urine. It can be prevented by administration of pyridoxine whenever isoniazid is given. A 10 mg. dose of pyridoxine for each 100 mg. of isoniazid appears adequate to prevent both clinical and potential subclinical manifestations of pyridoxine deficiency. The administration of pyridoxine does not interfere with the antituberculous action of isoniazid.

RESUMEN

La neuropatía periférica producida por la isoniacida en los tuberculosos adultos, es resultado de la deficiencia de piridoxina biológicamente activa. La deficiencia es causada por la combinación de la isoniacida con la piridoxina para formar hidrazona que se excreta en la orina. Puede evitarse administrando piridoxina cuando se dé la isoniacida. La dosis de 10 miligramos por cada 100 mg. de isoniacida parece adecuada para evitar tanto las manifestaciones clínicas como las potenciales subclínicas de la deficiencia piridoxínica.

La administración de la piridoxina no interfiere con la acción antituberculosa de la isoniacida.

RESUME

L'atteinte du système nerveux périphérique due à l'isoniazide, survenant chez des adultes tuberculeux provient d'une déficience en pyridoxine biologiquement active. La déficience est provoquée par l'association d'isoniazide et de pyridoxine qui forment un hydrazone qui est excrété dans l'urine. On peut l'empêcher par l'administration de pyridoxine même si on donne de l'isoniazide. Une dose de 10 mmgr. de pyridoxine pour 100 mmgr. d'isoniazide semble être la dose suffisante pour empêcher les manifestations cliniques et éventuellement subcliniques de la déficience en pyridoxine. L'administration de pyridoxine n'influence pas l'action antituberculeuse de l'isoniazide.

ZUSAMMENFASSUNG

Die durch INH bewirkte periphere Neuropathie, wie sie bei erwachsenen tuberkulösen Patienten auftritt, ist die Folge eines Fehlens von biologisch aktiven Pyri-

doxin. Dieser Mangel hat als Ursache die Verbindung von INH und Pyridoxin zur Bildung eines Hydrazons, das mit dem Urin ausgeschieden wird. Dies kann verhindert werden durch Gaben von Pyrazinamid, jedesmal, wenn INH verordnet wird. Eine 10 mmg-Dosis von Pyridoxin auf je 100 mmg INH scheint angemessen zur Verhinderung sowohl von klinisch wie potentiell subklinischen Manifestationen von Pyridoxinmangel. Die Verordnung von Pyrazinamid hat keinen störemden Einflus auf die antituberkulöse Wirkung von INH.

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SECTION ON CARDIOVASCULAR DISEASES

Untreated and Treated Patients with Hypertension*

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Effective agents for reducing blood pressure are available today. Because of the incidence of side-effects and the problems associated with the use of these drugs, the clinician is justified in raising the question as to their therapeutic efficacy, particularly whether the blood pressure reduction as such will alter the course of the disease and the prognosis of patients with hypertension. Consequently, in this presentation we shall present some data on the effect of blood pressure on vital vascular beds throughout the body and the response to blood pressure reduction in these areas. Subsequently, the primary problems associated with the use of anti-hypertensive drugs will be considered.

The Course of the Disease

Nearly all investigators who have studied the problem of hypertension agree that blood pressure elevation damages the vascular system in numerous vital vascular areas, particularly the heart, the brain and the kidney. When appraising the degree of altered function in these areas, it is difficult to evaluate cerebral function and cardiac function by specific measurements. For example, electrocardiographic changes are seen in the majority of patients with severe hypertension, but it is difficult to quantitate these changes.

The kidney is one of the most, if not the most, sensitive organ to vascular changes resulting from hypertension. In addition, renal function can be quantitated by an estimation of glomerular filtration rate and renal blood flow. Thus, one can quantitatively estimate the renal reserve and

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TABLE I—FOLLOW-UP IN 31 PATIENTS WITH MALIGNANT HYPERTENSION

Cause of Death	13 Treated 11 Living 2 Dead	18 Untreated 1 Living 17 Dead
CVA	1	3
CVA + Uremia	1	1
Uremia	0	11
Cardiac Failure	0	2
Avg. Survival time (months) or follow-up period if living	30	14

CVA = cerebrovascular accident

the functioning capacity of the kidney. By using these techniques, we have studied the effect of hypertension on the kidney in patients with elevated blood pressure, and we have studied also the effect of blood pressure reduction in patients with hypertension and compared these observations with those made on a similar group of patients who received no antihypertensive therapy for a period of three to five years.[1, 2]

Observation of renal function in 129 patients who reported to the clinic for treatment are summarized in Figure 1. None of them had effective treatment for hypertension prior to this study. The blood pressure in these patients was measured by direct intra-arterial manometry in order to avoid errors associated with auscultatory blood pressure recordings. Glomerular filtration rate was estimated by the use of inulin clearance.[3] The mean arterial blood pressure has been plotted against glomerular filtration rate in these patients (Figure 1). The numbers encircled on the graph indicate the number of patients at each level of arterial blood pressure. It is quite obvious that the higher the arterial blood pressure the lower was the glomerular filtration rate, indicating an inverse relationship between glomerular filtration rate and blood pressure elevation. In other words, the higher the blood pressure, the greater was the renal damage and the less was the renal reserve for the overall group of patients.

Figure 2 presents a diagrammatic concept of the overall vasoregulatory mechanisms as they affect blood pressure. Numerous factors come to

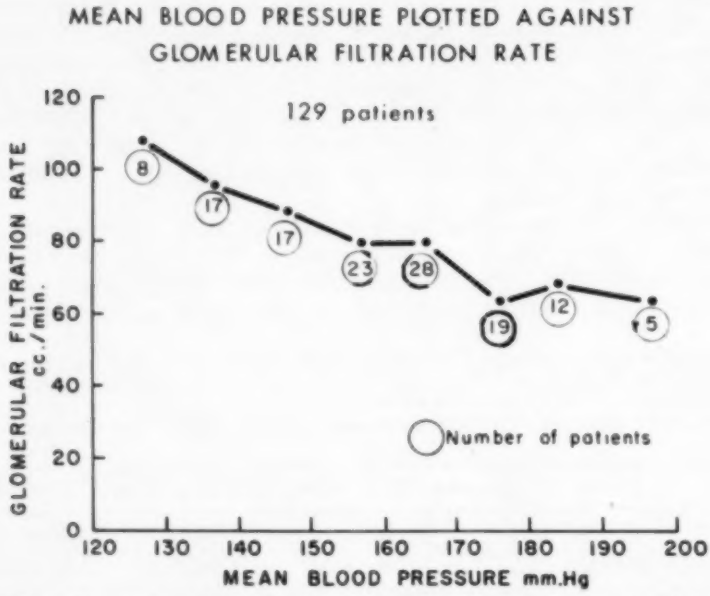

FIGURE 1: The average values for glomerular filtration rate compared to increasing severity of hypertension, as estimated by increased arterial blood pressure. Length of history of having had the disease was not considered. There is a greater reduction in glomerular filtration rate in those patients who show the greatest increase in blood pressure, thus indicating a direct relationship between the severity of the hypertension and the renal vascular deterioration. The numbers in the circles indicate the number of patients with this blood pressure as measured by intraarterial manometry. (Courtesy Am. J. Med. 24:164, 1958.)

play in the regulation of blood pressure both in the normotensive (Figure 2A) and in the hypertensive individual (Figure 2B). Thus, such factors as environmental stimuli, circulating humoral agents, and emotional factors, all have their effect on the hypothalamic area and secondarily, on the vasoregulatory areas. By altering the outflow of vasoconstrictor impulses from the vasoregulatory areas, the blood pressure increases or decreases accordingly, depending on the degree of constriction of the arterioles throughout the body. In the hypertensive patients, the outflow of vasoconstrictor impulses is increased or the responsiveness of the blood vessels is increased above normal. Sodium chloride seems to increase the responsiveness of the blood vessels to vasoconstrictor impulses. The increase in blood pressure causes vascular degenerative changes i.e. enhancement of arteriosclerosis, renal vascular degeneration, heart failure, coronary sclerosis, and cerebral vascular damage. It is probable that the blood pressure elevation effects all of these factors in an adverse fashion. Furthermore, it is also probable that by controlling the blood pressure, the degenerative factors associated with blood pressure elevation will be arrested or at least the tempo of their progression will be slowed. The following observations give us an estimate of the effect of treatment on vascular degenerative changes.

Malignant Hypertension: Patients with a malignant hypertension show a rapidly deteriorating clinical course. The majority of untreated patients are dead within 8 to 10 months, and less than 10 per cent of patients with malignant hypertension survive for more than 2 years when not treated (Table I). Table II summarizes the follow-up observations on renal hemodynamics and clinical manifestations in 21 patients who were admitted to the clinic with malignant hypertension. The average follow-up in the

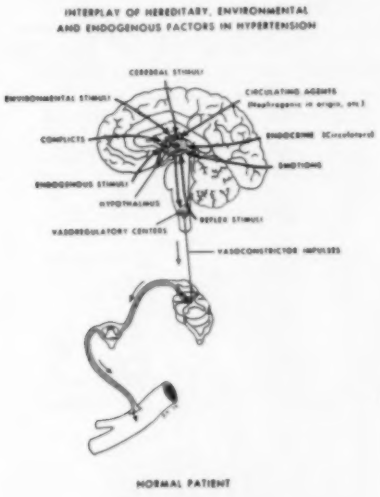

FIGURE 2A

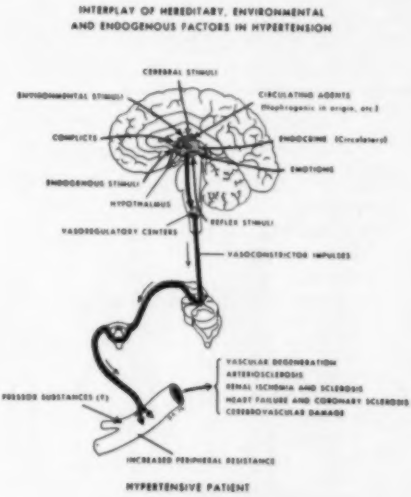

FIGURE 2B

Figure 2A: Diagrammatic representation of a normal patient with a normal outflow of vasoconstrictor impulses over the sympathetic nervous system.—*Figure 2B:* Patient with hypertension. The outflow of vasoconstrictor impulses is increased or the blood vessel is overly responsive to the normal outflow of vasoconstrictor impulses. In either event the blood pressure increases to hypertensive levels.

treated patients was 28 months and in the untreated patients was 10 months. The reason for the short follow-up in the untreated patients was due to the fact that all but one of them died in less than 1 year.

It is quite obvious that in the treated group of patients (Table II), the glomerular filtration rate prior to therapy and after two years of therapy was essentially the same for the overall group of patients. Renal blood flow was also not altered significantly. The mean blood pressure was reduced from 175 mm. of mercury to 122 for the group. This is in sharp contrast to the patients who were not treated (Table II). Renal damage was progressive in these patients as indicated by an average reduction in glomerular filtration rate from 70 cc.'s per minute to 44 cc.'s per minute. Renal blood flow was reduced proportionally. This was associated with a progressive renal failure as indicated by an overall rise in BUN from 29 mg. per cent to 106 mg. per cent.

Figures 3 and 4 are typical case examples of patients with malignant hypertension. Figure 3 is an untreated patient with hypertension showing the progressive reduction in glomerular filtration rate and renal blood flow. This patient died 18 months after the initial study. By comparison, Figure 4 is a patient who was treated adequately. When the control observations are compared with the estimated normal observations for this patient, there is evidence that the kidneys were severely damaged prior to therapy so that the values for this patient were 45 per cent (glomerular filtration rate) and 35 per cent (renal blood flow) of the estimated normal values. Despite the evidence of severe renal damage that had occurred prior to therapy in this patient, when the patient was treated effectively for four years, glomerular filtration rate and renal blood flow did not decrease any farther. In other words, the renal vascular deteriorating effect was arrested by therapy but it did not return to or towards normal. This

TABLE II—COMPARISON OF FOLLOW-UP RENAL STATUS IN TREATED AND UNTREATED MALIGNANT HYPERTENSIVES—21 PATIENTS

	Treated		Untreated	
	No.	Per Cent	No.	Per Cent
No. of Patients	12	57	9	43
Mortality	2	17	9	100
Survival Time or follow-up period (if living)	29 months		12 months	
Average	C	D_1	C	D_1
Laboratory observations (averages)				
BUN mg.%	31	27	29	106
GFR cc./min.	66	68	70	44
RBF cc./min.	513	579	628	351
MBP mm. Hg.*	175	122	184	197
Duration (C-D_1)	28 months		10 months	
Per Cent Improved				
Urinalysis	36		0	
ECG	54		0	
X-Ray	54		0	

C—Control Observations
D_1—Post Drug Observations
GFR—Glomerular Filtration Rate
RBF—Renal Blood Flow
MBP—Mean Arterial Blood Pressure

*Mean blood pressure (diastolic + ⅓ pulse pressure).

indicates that blood pressure reduction in patients with malignant hypertension will arrest the vascular deteriorating effect that occurs in the kidney but the renal function will not return to normal. Therefore, it is essential that if treatment is to be effective, the patients will have to receive blood pressure reduction before the point of no return has been

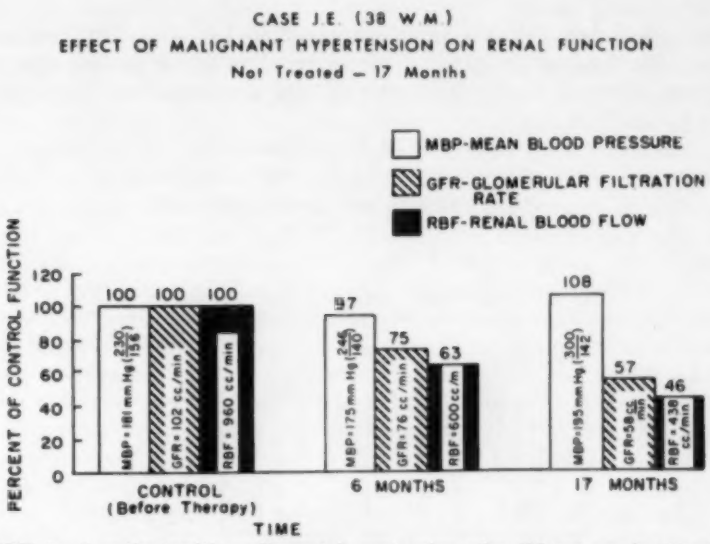

FIGURE 3: A patient with malignant hypertension who did not receive treatment, renal function deteriorated progressively. (Courtesy Am. J. Med. 24:177, 1958.)

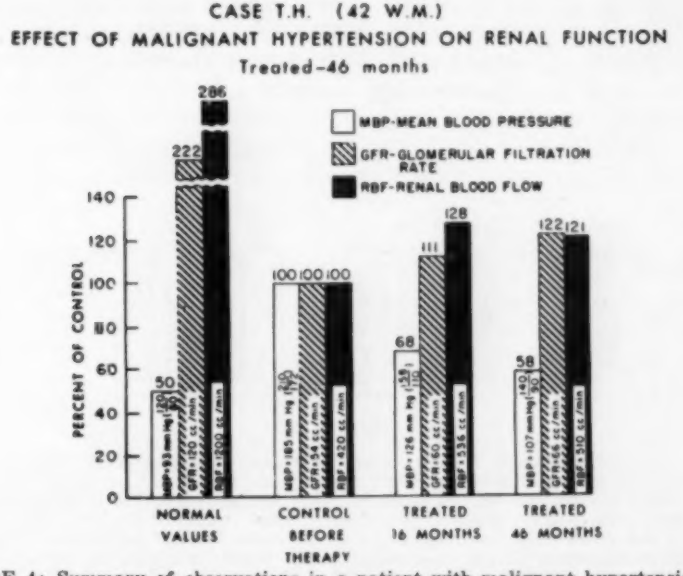

FIGURE 4: Summary of observations in a patient with malignant hypertension who was treated effectively. The vascular degenerative process in the kidneys was arrested by blood pressure reduction. (Courtesy Am. J. Med. 24:177, 1958.)

reached, since significant improvement in renal function cannot be expected in most patients.

The causes of death in 19 of 31 patients with malignant hypertension are recorded in Table I. Not any of the patients with malignant hypertension who were treated adequately died from uremia. By comparison, of the 18 patients who were not treated for malignant hypertension, 11 died with renal failure.

Observations on patients with hypertension but not of the malignant variety: Eighty-four patients on whom renal function studies were done have been followed for 2 years or more with non-malignant hypertension.

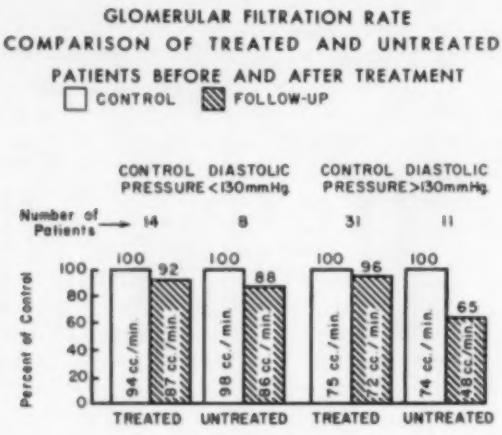

FIGURE 5A

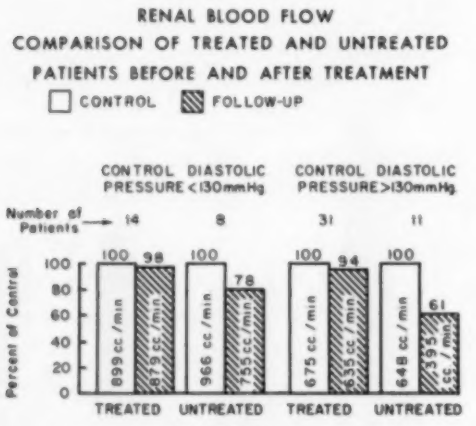

FIGURE 5B

Figure 5A: Comparison of the effects of hypertension on glomerular filtration rate in treated and untreated patients with hypertension. There was no significant difference in the patients with control diastolic pressures less than 130 mm. Hg. But in the patients with control diastolic pressures of more than 130 mm. Hg., the patients who were not treated showed progression of the renal damage as reflected in further reduction in glomerular filtration rate but in the treated patients, the renal vascular deterioration was arrested.—*Figure 5B:* The effect on renal blood flow was similar to the effect on glomerular filtration rate (Figure 5A). (Courtesy Am. J. Med. 24:177, 1958.)

Figures 5A and 5B compare the pre-treatment values for glomerular filtration rate and renal blood flow in treated and untreated patients. The patients in group I had a diastolic pressure of more than 100 but less than 130 mm. of mercury prior to treatment. The patients in group II had a diastolic pressure of greater than 130 mm. of mercury. The pre-treatment status of the patients in the treated and untreated patients for both groups I and II was quite similar.

When the treated patients in group I (diastolic less than 130 mm. of mercury) are compared with the untreated patients after 2 years follow-up, it is apparent that there was very little difference since the glomerular filtration rate was not reduced significantly in either the treated or the untreated patients. However, there was a sharp contrast in the patients who had a diastolic pressure of more than 130 mm. of mercury prior to therapy. In the untreated patients the glomerular filtration rate decreased from 74 cc.'s per minute to 48 cc.'s per minute or to 65 per cent of the control value. By contrast in the treated patients, there was no further reduction in glomerular filtration rate. Both the treated and the untreated patients in this group had shown a significant degree of vascular damage in the kidneys prior to therapy since glomerular filtration rate was only about three-fourths of the normal value for this function. Therefore, again we see that renal function as estimated by glomerular filtration rate did not return to normal with blood pressure reduction but the vascular deteriorating effect was arrested and therefore, glomerular filtration rate did not decrease any farther.

Renal blood flow followed the same course as glomerular filtration rate. After two years or more of follow-up in the untreated patients with a diastolic of more than 130 mm. of mercury, there was a continued reduction in this function. By contrast in the treated patients, the values were essentially the same as they were prior to therapy. Here again, there is evidence that the disease process was arrested.

Clinical observations in a group of 129 patients indicates that 44 of them have died 2 to 5 years after the study was initiated. The causes of death in these patients is summarized in Table III. A few very interesting observations are herewith recorded. None of the patients in the treated

TABLE III—CAUSES OF DEATH IN 44 PATIENTS WITH NON MALIGNANT HYPERTENSION

Cause of Death	Number (Total)	Treated No.	Treated Per Cent	Untreated No.	Untreated Per Cent
Uremia	15	0	0	15	100
CVA	19	9	47	10	53
Cardiac	4	0	0	4	100
CVA with Uremia	3	1	33	2	67
Others	3	1	33	2	67
Total	44	11	25	33	75
Avg. Survival Time (months)		22		11	
Avg. BUN. mg.% Control		30		46**	
Avg. GFR cc./min. Control		68		56	
Avg. RBF cc./min. Control		616		515	
Avg. MBP mm. Hg.* Control		169		170	

*Mean blood pressure (diastolic + ⅓ pulse pressure).
**This value is high by virtue of 2 patients having marked elevation in the BUN: If these 2 patients are not included the average BUN would be 36.

TABLE IV—OUTLINE FOR ANTIHYPERTENSIVE TREATMENT OF HYPERTENSIVE EMERGENCIES

Initial Therapy

Emergency	Drug	Dose	Route	Frequency	Adjunctive Therapy when Initial Drug Inadequate	Maintenance Therapy After Emergency Over
Encephalopathy	Reserpine or Rescinnamine	2.5 to 10 mg. 5 to 15 mg.	I.M. I.M.	4-12 hours 4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate then Veriloid titration I.V. infusion	Rauwolfia + Ganglionic blocking agent + chlorothiazide
Fulminating Heart Failure with severe hypertension	Hexamethonium or Arfonad	10 to 100 mg. Titration	I.M. I.V.	30 min. to 4 hours Continuous infusion	Reserpine I.M. or Veriloid titration by I.V. infusion	Rauwolfia + Ganglionic blocking agent + chlorothiazide
Intractable Angina with Severe Hypertension	Hexamethonium		I.M.	1-4 hours	Reserpine 2.5 to 10 mg. given I.M.	Rauwolfia + Ganglionic blocking agent + chlorothiazide
Hypertensive Crisis	Reserpine or Rescinnamine	2.5 to 10 mg. 5 to 15 mg.	I.M. I.M.	4-12 hours 4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate response then Veriloid by I.V. infusion	Rauwolfia + Ganglionic blocking agent + chlorothiazide
Malignant Hypertension of Renal Origin*	Reserpine or Rescinnamine	2.5 to 10 mg. 5 to 15 mg.	I.M. I.M.	4-12 hours 4-12 hours	Hexamethonium 10-100 mg. I.M. If inadequate response then Veriloid by I.V. infusion	Rauwolfia + Ganglionic blocking agent + chlorothiazide

*Cystic disease, pyelonephritis, renal artery occlusion, etc.

group who died were in renal failure but 15 patients died in renal failure in the untreated group. The most frequent cause of death in patients who died despite anti-hypertensive therapy was cerebrovascular accident.

Summary of Therapeutic Approach to Hypertensive Emergencies

In a patient with a hypertensive emergency associated with severe essential hypertension, it is necessary first to appraise the state of renal compensation, particularly if cerebration is abnormal. This can best be done with an estimate of the blood urea nitrogen (BUN). If the blood urea nitrogen is normal, renal failure is not likely to be responsible for any disturbances in the sensorium.

Retinal examination also helps. Retinal hemorrhages indicate the degree of general arteriolar damage. Papilledema suggests increased intracranial pressure and cerebral edema, which frequently accounts for derangement of cerebral function in patients who do not have associated renal failure.

After the state of renal function is known, therapy should be approached systemically (Table IV). If immediate blood pressure reduction is not indicated and a delay of two to three hours is possible, parenteral reserpine or rescinnamine is usually the drug of choice. The initial dose of reserpine* is 2.5 mg., and of rescinnamine is 5 mg. repeated in two hours if blood pressure reduction is not adequate. The dose is progressively increased at 4 hour intervals until the blood pressure is reduced adequately or the maximum dose has been reached. When establishing maintenance therapy the drug should be given as infrequently as possible and at a dose as small as possible to keep the blood pressure at the desired level. When the blood pressure is not reduced adequately at a maximum dose of 10 mg. of reserpine or 15 mg. of rescinnamine, given every six hours, a ganglionic-blocking agent should be tried.

There is very little difference in responsiveness among the different ganglionic-blocking agents. We prefer hexamethonium for initial therapy because of its shorter duration of action. If the response does not appear beneficial, the drug can be discontinued with the loss of blockade in two to three hours. The initial dose of hexamethonium is 15 mg. This can be repeated in one hour and the dose increased as necessary. When the blood pressure response is not adequate at a dose of 100 mg. it is useless to increase the dose any farther. In patients with fulminating heart failure or intractable angina pectoris, the ganglionic blocking agent should be given first.

In the case of fulminating heart failure a continuous infusion of Arfonad is probably the therapy of choice if hexamethonium is not adequate. Care must be taken so that excessive fluid is not administered. When ganglionic blockade appears to be adequate, one of the longer acting agents can be substituted for the hexamethonium after two or three days. This allows for less frequent administration.

When ganglionic blocking agents given in combination with reserpine are not adequate, parenteral Veratrum should be given. Continuous infusion is the most potent and most effective approach, but the intramuscular route is preferred when full-time competent nursing care is not

*Supplied to the authors as Sandril by Eli Lilly & Co.

available, since excessive hypotensive episodes are less likely to occur following intramuscular administration.

After the blood pressure has been stabilized for three to seven days and the general status of the patient seems adequate, a permanent-type program for blood pressure regulation should be substituted for the parenteral medication. A combination of chlorothiazide (500 mg. every 12 hours by mouth) and rauwolfia should be tried first. When this is not adequate, a ganglionic blocking agent should be added to the therapeutic regimen. A dose of rauwolfia of 1 mg., of reserpine, 250 mg. of the whole root or 8 mg. of alseroxylon is usually given orally. After several weeks this dose can be reduced in half.

As the effect of chlorothiazide becomes established, the parenteral reserpine should be discontinued. As the effect of the parenteral reserpine is lost, one of the blocking agents is started and the dose gradually increased. The dose of the blocking agent must be adjusted according to the standing blood pressure. It is preferable to have the patient completely ambulatory while adjusting the drugs administered orally.

Results obtained in patients who have a normal BUN are superior to those obtained when the BUN is increased above normal (Table V). When the BUN is elevated, this determination should be repeated every 2 or 3 days while the blood pressure is being regulated. When evidence of a rising blood urea nitrogen is observed, the pressure should be allowed to increase slightly by decreasing the dose of the blocking agent until the blood urea nitrogen again decreases to pre-treatment levels. As the blood pressure is controlled for prolonged periods, progressive vascular deterioration is usually arrested, and renal function will usually improve if it has not passed the point of no return.

Treatment of the Ambulatory Patient

There are two (2) important aspects of anti-hypertensive therapy. These are suppression of sympathetic impulses traveling from the brain to the blood vessels and depletion of the body stores of sodium. The latter can be accomplished by decreasing the intake of sodium or increasing the excretion rate through the use of diuretics.

TABLE V—SUMMARY OF RESULTS OBTAINED IN PATIENTS RECEIVING RESERPINE GIVEN PARENTERALLY FOR SEVERE HYPERTENSIVE ENCEPHALOPATHY WITH AND WITHOUT RENAL DAMAGE

	Patients with Normal BUN	Patients with Azotemia but nonuremic	Patients in Uremia
Number patients treated	8	10	16
Number with papilledema (before R)	8	9	13
Number responding*	8	8	14
Number normotensive**	5	6	12
Aggravation renal failure	0	3	12
Number living after three months	8	6	6

*Reduction in mean blood pressure of 20 mm. Hg. or more.
**Blood pressure reduced below 150/100.

Diuretic Therapy: Sodium chloride has long been considered as an important aspect of essential hypertension since increased intake of sodium aggravates hypertension and a low intake of sodium chloride improves the hypertensive state. However, because the sodium intake which will pro-

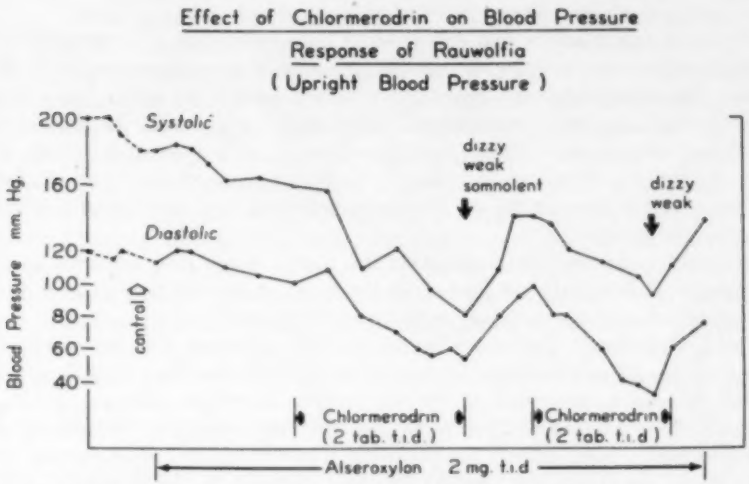

FIGURE 6: Blood pressure response to alseroxylon in a patient with hypertension with and without concurrent administration of chlormerodrin, a mercurial diuretic. The blood pressure reduction was significantly enhanced by the administration of chlormerodrin, apparently due to the diuretic and natriuretic effect of the mercurial diuretic. When the mercurial was withdrawn the blood pressure again increased.

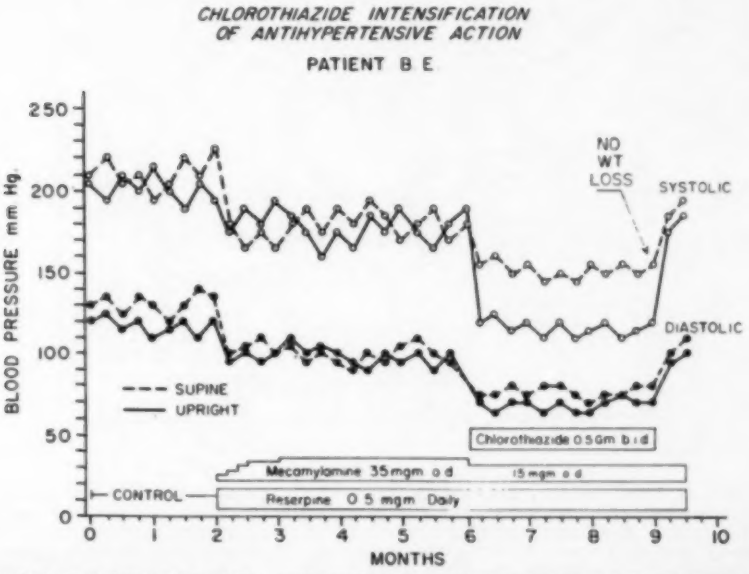

FIGURE 7: Potentiation of the orthostatic hypotensive response to mecamylamine by chlorothiazide. This occurred in the absence of any weight loss. When the chlorothiazide was withdrawn there was a sharp rise in blood pressure. (Courtesy *Ann. N. Y. Acad. Sci.*, 71:456, 1958.)

duce these is so low, the food becomes quite unpalatable, consequently from a practical point of view, this form of therapy is rarely successful.

Diuretic therapy in itself is usually not successful in reducing blood pressure but when used in conjunction with drugs which block the sympathetic nervous system diuretics become an integral part of the medical management of the patient with hypertension.

Figure 6 summarizes the response to chlormerodrin (Neohydrin) in a patient who was previously receiving alseroxylon (Rauwiloid) but in whom the blood pressure response was not adequate, when the diuretic was started the blood decreased significantly. In order to obtain this response with chlormerodrin, it is necessary to give at least 2 tablets with each meal, i.e., three times a day. Unfortunately nausea and diarrhea are seen fairly frequently on this dose schedule and the therapy has not been too popular.

Recently a nonmercurial diuretic has been introduced for oral administration. It is equally as potent as the mercurial diuretic and is remarkably free of serious side effects in patients with hypertension. Consequently, it is more useful as an adjunctive measure for increasing the effectiveness of sympathetic nervous system depressants (Figs. 7 and 8).

Figure 9 is a summary of the electrolyte excretion pattern of chlorothiazide. The primary effect is to increase the excretion of sodium and chloride with lesser effects on potassium and bicarbonate excretion. The

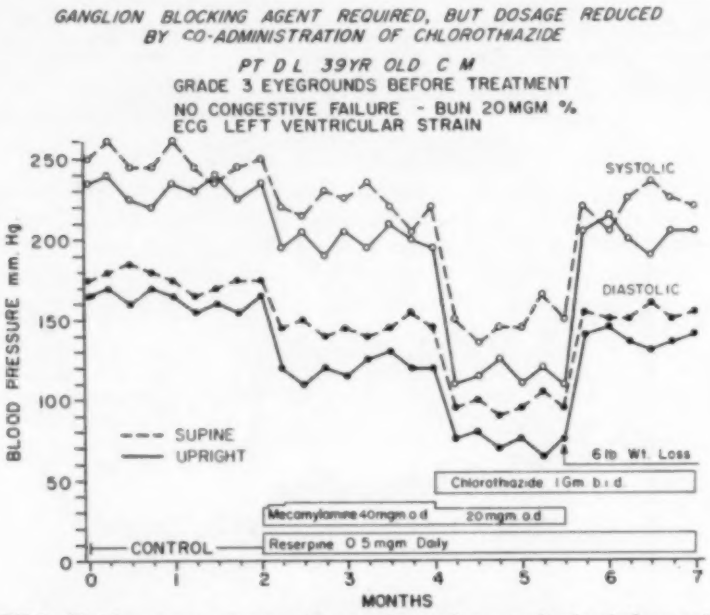

FIGURE 8: Blood pressure response to reserpine and mecamylamine before and after the concurrent administration of chlorothiazide. Although there was a significant reduction in blood pressure prior to the administration of chlorothiazide, this response was markedly increased when chlorothiazide was given. However, when the mecamylamine was temporarily withdrawn the blood pressure quickly rose to nearly control levels despite the continued administration of chlorothiazide in conjunction with reserpine. This case demonstrates the necessity of continuing the ganglionic blocking agents despite the administration of chlorothiazide in many patients (Courtesy *Ann. N. Y. Acad. Sci.*, 71:456, 1957.)

drug continues to produce natriuresis with continued administration (Figure 10) and it is as effective by the oral route as by the intravenous one.

In the management of patients who have not been treated previously, a recommended therapy is to restrict the salt intake moderately by not salting the food either when cooking or at the table. Obviously, salty food should be avoided. The patient should then be started on 250 mg. of chlorothiazide twice daily (every 10 to 12 hours). After three days this dose can be increased to 500 mg. given twice a day. The chlorothiazide should be continued indefinitely and without interruption at this dose level.

Rauwolfia in combination with chlorothiazide: After receiving the diuretic for one week, rauwolfia should then be started. Because of the lower incidence of side effects, we prefer alseroxylon* or the whole root over reserpine. When the alseroxylon fraction is employed, the patient should be given 2 mg. (1 tablet) with each meal and at bedtime for one week. Then the dose is reduced to 2 mg. twice a day. Should the patient prefer to take the alseroxylon all at one dose, there is no serious objection to doing so.

We prefer to give the drug in divided doses as a preliminary training period to taking drugs with meals, thus developing the habit pattern. Although, it is not critical that the rauwolfia compounds be taken regu-

*Rauwiloid—supplied by Riker Laboratories.

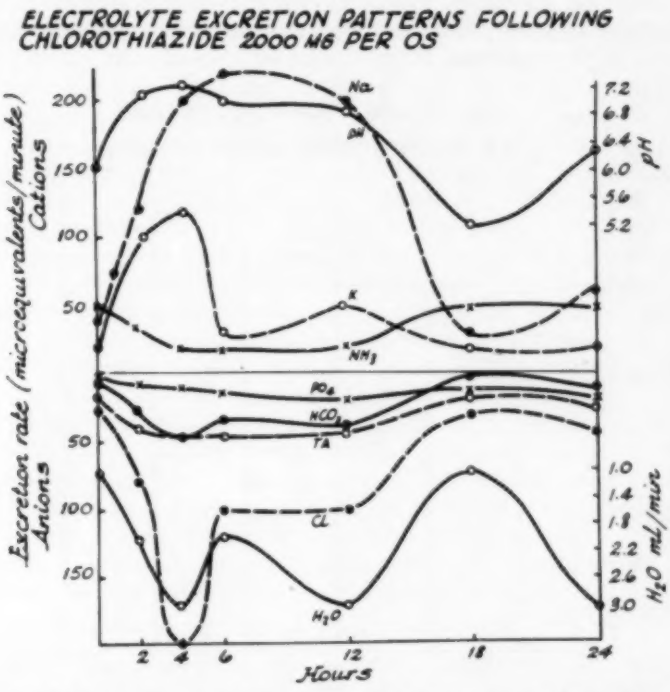

FIGURE 9: Electrolyte excretion patterns following 2000 mg. of chlorothiazide given orally. The greatest responses are observed in the excretion of sodium and chloride accompanied by an alkaline urine. The rate of bicarbonate excretion is increased, but the total excretion is small. There is a prompt onset and short duration of action. Potassium excretion is increased but not to the same extent that sodium excretion is increased. (Courtesy A.M.A. Arch. Int. Med. 100:582, 1957).

larly and exactly as directed, it is highly essential that this be done when the ganglionic blocking agents are employed.

Patients with fixed control diastolic arterial pressures of more than 120 mm. Hg. who do not respond adequately to this regimen of chlorothiazide and rauwolfia after one month should receive a ganglionic blocking agent in addition. This is particularly indicated when there is evidence of vascular degenerative changes resulting from the hypertension.

Adjunctive Therapy with Ganglionic Blockade: In the treatment of moderate to severe hypertension, the experience of most investigators suggests that chlorothiazide and rauwolfia given in combination with ganglionic blockade, i.e., either hexamethonium, pentolinium, chlorisondamine or mecamylamine, offers the most effective means for reducing the blood pressure. This combination also represents by far the most difficult of the commonly employed regimens to control, unless meticulous attention is given to such details as control of constipation, careful dose titration, and a thorough evaluation of the patient's symptoms during therapy. There is essentially no difference between chlorisondamine (Ecolid) and pentolinium (Ansolysen) ; the incidence of side effects, blood pressure response and the normotensive rates are about the same. Both of these agents are considerably more potent than hexamethonium and have a longer duration of action. Therefore, they are to some degree easier to use than hexamethonium. However, insofar as the incidence of side effects is concerned, there is little difference between hexamethonium and the other ganglionic blocking agents.

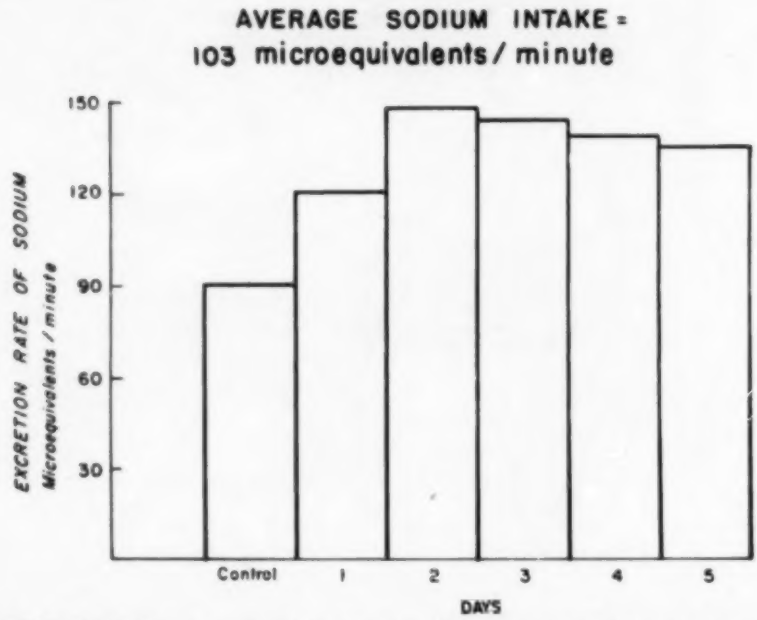

FIGURE 10: Sodium excretion following the administration of chlorothiazide, 2000 mg. single dose on five consecutive days, while nonedematous patient is eating a diet containing 150 mEq. of sodium per 24 hours. There is a continued response to the daily administration of chlorothiazide. (Courtesy A.M.A. Arch. Int. Med. 100:582, 1957).

Recently, mecamylamine (Inversine) a new ganglionic blocking agent has become available. This is a secondary amine, rather than a quaternary ammonium compound. It is absorbed completely from the gastrointestinal tract, and in addition to producing ganglionic blockade, it has some central sedative effect. The duration of action is prolonged, frequently up to 36 hours. Despite the duration of action, greater potency, and complete absorption, as compared to the other ganglionic blocking agents, it still has the same side effects that are seen with quaternary ammonium compounds, i.e., parasympathetic blockade and frequent variability of blood pressure reduction. The latter results from the variability in sympathetic activity which patients display from time to time.

Special Problems Associated with the Use of Rauwolfia plus Ganglionic Blocking Agents:

Dose Titration:

There are some rules which must be observed when ganglionic blocking agents are used. One of the most important is adequate dose titration. It is necessary to start the patient on a small dose and increase it gradually until an appropriate dose, which produces the desired response, is obtained for each individual patient. This minimizes the incidence of side reactions and serves to prevent episodes of excessive reduction in blood pressure.

Constipation and Ileus:

Constipation, which may progress to ileus if untreated, or treated inadequately, can be a serious problem with the use of any ganglionic blocking agent. It is essential that strict attention be given to this problem, and that cathartics and cholinergic agents be used freely. As with the blood pressure response, the constipating effect of the blocking agents is an individual response, and, as a result, the method for combating this problem must be individualized for each patient. The optimal approach for each patient must be determined by trial and error. In some patients the cholinergic agents such as prostigmine, in a dose of 15 to 30 mg. given orally before the meal, is quite adequate. However, in others this produces cramping in the abdomen and it is necessary to use cathartics such as 15 to 30 cc. of milk of magnesia or 10 to 15 cc. of cascara sagrada. If these are ineffective when used alone, then 30 cc. of milk of magnesia and 15 cc. of cascara sagrada given together rarely fails.

Should ileus develop due to ganglionic blockade, the patient should be hospitalized and treated actively. We have found that prostigmine, 1 mg. given parenterally every hour until bowel movement occurs and ileus is relieved, is always effective. to date, we have not observed any serious complications due to this problem although we are aware of the potential dangers, and consequently, each of our patients is duly warned prior to beginning therapy with any of the ganglionic blocking agents.

Renal Considerations with Blood Pressure Reduction:

The majority of patients who have had moderately severe to severe hypertension for prolonged periods of time will usually exhibit variable degrees of renal damage. This must be taken into consideration when initiating antihypertensive therapy. Effective reduction of blood pressure will usually prevent progressive anatomical damage to the kidney, but, at the same time, the physiology of renal function is such that some re-

duction in glomerular filtration rate usually accompanies the acute reduction in blood pressure. This is usually temporary and returns to the pretreatment levels after hemodynamic readjustment takes place if the degree of blood pressure reduction is not excessive. Generally speaking, the less the renal damage, prior to induction of therapy, the better the patient will tolerate blood pressure reduction. For example, if glomerular filtration rate is adequate, then the blood pressure can be reduced to normotensive levels without fear of renal decompensation. However, if glomerular filtration is depressed severely prior to the induction of therapy, even a slight reduction in glomerular filtration rate may be deleterious. In these patients, it is necessary to reduce the blood pressure slowly, and to keep a close watch on the renal function. The blood urea nitrogen determination is the most effective and valuable laboratory aid to guide the therapist concerning the degree to which the blood pressure can be reduced, and still be tolerated safely by the patient with pre-existent renal disease.

When patients who are receiving ganglionic blocking agents are ambulatory, there is a greater reduction in renal function than is seen in the supine position. This should be considered if excessive reduction in blood pressure should occur with the use of these agents or if the patient develops progressive renal insufficiency. He should then remain in bed, and supine until this unfortunate complication has been corrected.

Table VI presents the general range to which the blood pressure can be reduced, without depressing renal function, in the majority of patients. It will be noted that the greater the elevation in blood urea nitrogen, the less effectively the blood pressure can be regulated. When the blood urea nitrogen is above 50, repeated determinations must be made as the blood pressure is being reduced. The blood pressure should always be regulated in the upright position. Whenever there is evidence that the blood urea nitrogen is rising, the blood pressure cannot be reduced any further and in fact, should usually be allowed to rise slightly. As noted above, a paradox exists in that (from a functional point of view) reducing the blood pressure in patients who have severely damaged kidneys, may cause some reduction in renal function, at the same time if an adequate reduction in pressure can be obtained, it will prevent progressive anatomical damage to the kidneys.

Should excessive reduction in blood pressure occur, associated with excessive depression in renal function, this can easily be corrected by the use of a vasopressor agent.

TABLE VI—APPROXIMATE DEGREE OF BLOOD PRESSURE REDUCTION (UPRIGHT) THAT CAN BE ACCOMPLISHED—DEPENDENT ON AMOUNT OF PRE-EXISTING RENAL DAMAGE

Blood Urea N/mg.%	Reduce Upright Blood Pressure to:
Normal	130-150/ 80-100
BUN 30 to 50	160-180/100-110*
BUN 50 to 100	180-200/110-120*
BUN 100	No Reduction

*Check BUN repeatedly during period of blood pressure reduction and do not reduce blood pressure further if BUN rises.

Early Morning Reactivity with the Use of Long Acting Ganglionic Blocking Agents: There are a few additional considerations in the use of these agents for the treatment of severe hypertension. For example, with the long acting ganglionic blocking agents, particularly with mecamylamine, it is necessary to give a larger dose in the morning, and at noon time. We have found that if we have patients who require large doses of the blocking agents and use equal doses througout the day, i.e., with meals and at bedtime, excessive reduction in blood pressure occurs when the patients first arise in the morning. They will complain of dizziness and weakness. However, when the dosage schedule is arranged so that a large dose is given to these patients at breakfest, and at lunch, and relatively small doses at supper time, without medication at bedtime, this early morning reactivity does not occur.

Variation in Environmental Stress: It is important to remember that when a ganglionic blocking agent is used, the degree of blockade is relatively fixed. Therefore if the patient is subjected to excessive stresses, the activity within the sympathetic nervous system will increase. As a result, more impulses will break through the ganglionic blockade and the blood pressure will rise. If periods of stress are to be anticipated, then the dose of the blocking agent will frequently have to be increased. On the other hand, if the patient who has been under stressful situations retires to a more relaxed atmosphere, it is frequently necessary to reduce the dose of the ganglionic blocking agent; otherwise, he will get excessive reduction in blood pressure since less vasoconstrictor impulses are emanating from the central nervous system and traveling over the sympathetic nerves to the blood vessels. It thus becomes necessary to stabilize the patient's life, emotions and environmental stresses. This can only be done by a therapist who is understanding and can offer every day psychiatric assistance to his patient.

SUMMARY

Observations have been made on renal hemodynamics in patients with hypertension. When the blood pressure was markedly elevated glomerular filtration rate was reduced consistently, indicating renal damage.

Effective reduction in blood pressure with anti-hypertensive drugs arrested the vascular deterioration associated with severe hypertension. This occurred in both patients with malignant hypertension and in those with non-malignant hypertension.

The drug therapy of hypertension can be divided into (1) the treatment of emergencies associated with severe essential hypertension and (2) the out-patient management of hypertension. As a general rule, reserpine given parenterally is the drug that should be used initially for treating emergency states. When this is not adequate a ganglionic blocking agent or a parenterally administered veratrum preparation should be used.

The treatment of ambulatory patients consists of pre-medication with chlorothiazide for depleting the amount of sodium in the body followed by drugs which depress the sympathetic nervous system. Of the sympathetic depressants, we prefer to use rauwolfia initially. When this agent, given in combination with chlorothiazide, is not adequate in any patient with severe and maintained blood pressure elevation, then a ganglionic blocking agent should be added to the regimen. Adequate precautions shou.d be taken to minimize the severity of the side reactions associated with the ganglionic blocking agents.

RESUMEN

Se han hecho observaciones hemodinámicas renales en enfermos con hipertensión. Cuando la presión sanguinea estaba muy elevada la filtración glomerular estaba disminuída indicando daño renal.

La reducción efectiva en la presión sanguínea por las drogas hipertensoras, detuvo el daño vascular que se asociaba a la hipertensión.

Esto ocurrió tanto en enfermos con hipertensión maligna como en aquéllos con hipertensión no maligna.

La terapéutica de la hipertensión puede dividirse en: (1) el tratamiento de las emergencias acompañadas de hipertensión severa y (2) los pacientes ambulatorios hipertensos. Como regla general la reserpina inyectada es la droga que debe usarse inicialmente en las emergencias. Cuando ésta no es adecuada, se usará un agente de bloqueo ganglionar o la inyección de una preparación de veratrum.

El tratamiento de los enfermos ambulatorios consiste en la medicación con Clorotiacida para obtener una depleción de sodio del cuerpo seguida de drogas depresivas del sistema nervioso simpático. De los depresores simpáticos preferimos la Rauwolfia inicialmente. Cuando este agente, dado en combinación con la Clorotiacida no es adecuado en cualquier enfermo con hipertensión severa sostenida, debe agregarse un agente de bloqueo ganglionar. Las precauciones adecuadas deben tomarse para disminuir las reacciones colaterales de los ganglioplégicos.

RESUME

Des observations ont été faites sur l'hémodynamique rénale chez des malades atteints d'hypertension. Dans la pression sanguine, nettement élevée, le taux de filtration glomérulaire était réduit de façon importante, indiquant un trouble rénal.

Une diminution effective de la pression sanguine par des médications anti-hypertensives stoppa la détérioration vasculaire associée à l'hypertension grave. Ceci survint à la fois chez les malades atteints d'hypertension maligne et chez ceux atteints d'hypertension non-maligne.

La thérapeutique médicamenteuse de l'hypertension peut être divisée en 1°) traitement des urgences que peut déterminer une hypertension essentielle grave, et 2°) traitement de l'hypertension du malade consultant non hospitalisé. En règle générale, la réserpine donnée par voie parentérale, est la médication qui devrait être utilisée au début pour le traitement des états d'urgence. Quand ce produit ne convient pas, on devrait utiliser un agent de blocage ganglionnaire ou une préparation de veratrum administrée par voie parentérale.

Le traitement des malades ambulatoires consiste en une pré-médication par la chlorothiazide, pour réduire la quantité de sodium dans le corps, suivie de médications qui calment le système nerveux sympathique. Parmi les calmants du sympathique, les auteurs préfèrent l'emploi d'abord du Rauwolfia. Quand ce produit, donné en association avec la chlorothiazide, ne convient pas à certains malades atteints d'une élévation de la pression sanguine grave et continue, on doit alors ajouter au régime un agent de blocage ganglionnaire. Des précautions convenables doivent être prises pour diminuer la gravité des réactions d'intolérance dues aux agents de blocage ganglionnaire.

ZUSAMMENFASSUNG

Es wurden Beobachtungen angestellt über die renale Hämodynamik bei Kranken mit Hypertension. War der Blutdruck beträchtlich erhöht, so war die glomuläre Filtrationsrate entsprechend herabgesetzt und wies auf einen Nierenschaden hin.

Eine wirksame Verminderung des Blutdruckes mit antihypertonischen Medikamenten brachte die mit schwerer Hypertension verbundenen Gefässverschlechterungen zum Stillstand. Dies betraf sowohl Patienten mit malignem Hochdruck als auch solche mit nicht malignem Hochdruck.

Die medikamentöse Therapie der Hypertension kann gegliedert werden in (1) die Behandlung akuter Notfälle, wie sie bei schweren essentiellen Hochdruck vorkommen, und (2) die ambulante Betreuung des Hochdrucks. Nach der allgemeinen Auffassung ist das parenteralgegebene Reserpin das Mittel, das zu Beginn bei der Behandlung von akuten Zwischenfällen verabfolgt werden sollte. Erweist sich dieses als nicht wirksam, muss zu einem ganglien Blockherz oder einem parenteral zugeführten Niesworts-Präparat gegriffen werden.

Die Behandlung ambulanter Patienten besteht in einer Prämedikation mit Chlorothiazit zur Behebung des Natriumüberschusses im Körper und daran schliessen sich Mittel an, die auf das sympatische Nervensystem beruhigend wirken. Von den Sympathikus entspannenden Medikamenten ziehen wir es vor mit Rauwolfia zu beginnen. Ist dieses Mittel bei Verabfolgung zusammen mit Chlorothiazit nicht adequate bei einem Kranken mit schwerem und fixiertem Bluthochdruck, muss man einem ganglien Blockherz dem Behandlungschema hinzufügen. Entsprechende Vorkehrungen müssen getroffen werden, um die Schwere der mit den ganglien Blockherz verbundenen Nebenwirkungen möglichst zu verringern.

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A Classification of Elective Cardiac Arrest for Open Heart Surgery

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After the early successful intracardiac operations, it became obvious that coronary air embolism, exposure of the pathologic anatomy, and cardiac blood loss were problems still in need of solution. Elective cardiac arrest with the addition of bilateral pulmonary hilar tourniquets seemed clearly to answer such a need, but the most favorable method for producing circulatory arrest was not immediately apparent.

Under the heading of cardiac arrest, two rather different types were considered, ventricular fibrillation and cardiac standstill. Since the reversibility of ventricular fibrillation was well known to surgeons, it is not surprising that induced fibrillation received first trial. A quiet heart free from the hazard of coronary air embolism was attained through the expedient of ventricular fibrillation, but surgical fields remained obscure due to the necessity for coronary perfusion, and diminutions in blood loss were unimpressive. Standstill emerged as the most advantageous form of elective cardiac arrest.

I. Ventricular Fibrillation

In 1850 Hoffa and Ludwig[1] found that ventricular fibrillation could be induced electrically. Prevost and Batelli in 1899[2] demonstrated the abolition of ventricular fibrillation by electrical countershock. Hooker and his associates[3] quantitated these earlier observations and showed that fibrillation or defibrillation of the ventricles depended on the strength of the stimulating current. Weak shocks tend to fibrillate the heart while shocks of one ampere or more produce defibrillation. Leeds et al.[4] confirmed this work in 1951. Wiggers[5] classical definition of a vulnerable period late in systole was one of the most important contributions to the subject of ventricular fibrillation. Brooks, Hoffman, Suckling, and Orias[6] have studied cardiac excitability with precision electronic techniques which only now are becoming available for the analysis of ventricular fibrillation.

Senning[7] reported on the experimental use of induced ventricular fibrillation at normal temperature with the heart-lung machine which later included a human case operated upon by Crafoord.[8] Juvenelle[9] combined ventricular fibrillation, hypothermia, and the oxygenator with notably poor survival rates in experimental animals. Southworth and Pierce[10] and Glenn and Sewell[11] utilized ventricular fibrillation in their experiments to prevent coronary air embolism. Dennis is the most recent advocate of ventricular fibrillation during cardiopulmonary bypass. Induced ventricular fibrillation has also been used experimentally with hypothermia alone. When Jardetsky, Greene, and Lorber[12] showed that ventricular fibrillation actually increased myocardial oxygen consumption, very little enthusiasm endured for ventricular fibrillation as a form of elective cardiac arrest.

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Partially as a result of these varied observations, cardiac surgeons no longer fear ventricular fibrillation and seldom make any attempt to abolish the arrhythmia before completing the intracardiac procedure. The need for coronary perfusion while fibrillation persists is generally recognized.

II. Profound Hypothermia

Succeeding several reports of profound hypothermia with cardiac standstill in experimental animals, Niazi and Lewis[13] recently described a human case cooled to 9°C. and successfully rewarmed after one hour of circulatory standstill. Gollan and his co-workers[14] recorded experiences with deep hypothermia in animals with low percentages of retrieve. Heart action ceases at temperatures above freezing, but no application has been made of this fact with reference to cardiac surgery. Behavior of the supercooled heart is unpredictable even if standstill is achieved without ventricular fibrillation. Irritability of the heart at temperatures below 25°C. predisposes to ventricular fibrillation, and cardiac manipulation at near freezing is highly productive of this phenomenon. Many attempts have been made to diminish the incidence of ventricular fibrillation during moderate degrees of hypothermia, but none has been uniformly successful.

III. Vagal Stimulation or Simulation

In 1845 at the meeting of Italian Scientific Investigators, Ernst Heinrich Weber and his brother, Eduard, demonstrated for the first time an inhibitory effect from stimulation of a nerve. That nerve of course was the vagus, and its cardiac effect astounded the audience because never had excitation of a nerve provoked other than a strengthened or accelerated muscle action. The roles of acetylcholine and cholinesterase were ultimately delineated so that both acetylcholine and the anti-cholinesterases came to play a part in elective cardiac arrest.

Lam[15] and Moulder[16] support the use of acetylcholine to inhibit or stop cardiac activity for varying periods of time during open heart surgery, but others are bothered by random ventricular contractions which develop from mechanical stimulation of the heart.

Swan has worked at length with the anti-cholinesterase, prostigmine, and routinely employs the drug during cardiac occlusion under hypothermia with the firm conviction that the frequency of ventricular fibrillation is reduced.

IV. Potassium Standstill

Sidney Ringer wrote in 1883,[17] "I have not been able to discover a mixture consisting of saline solution, sodium bicarbonate solution and potassium solution which will keep the ventricle beating for more than a short time, although I have mixed these solutions in very various proportions . . . by increasing the quantity of potassium salt the beat becomes weaker and weaker till it stops." Several years later in 1907 at the meetings of the International Physiological Congress in Heidelberg, Hering[18] showed recovery from ventricular fibrillation in the isolated heart preparation with a few milliliters of 1 or 2 per cent potassium chloride solution injected into the perfusate. This method of chemical defibrillation was utilized in closed chest animal experiments by Hooker in 1929.

These writings provided the background for Melrose[19] and Lam[20] to report independently in 1955 the use of potassium citrate and potassium

chloride respectively for elective cardiac standstill. Effler and Kirklin adopted the method immediately and were joined eventually by others interested in the surgical correction of cardiac anomalies.

At Minnesota Lillehei with the widest experience in open heart surgery feels the least need for intentional cardioplegia. He prefers potassium citrate in the 2.5 per cent solution recommended by Melrose. Lillehei usually opens the heart first to ascertain if the anatomic complexity requires cardiac arrest. Occasionally extreme blood loss due to an incompetent aortic valve or prodigious bronchial return via the pulmonary circuit constitutes an emergency demand for cardiac standstill.

It is a gratifying fact that surgeons who use intentional cardiac arrest are becoming interested in the mechanism of action of potassium at the membrane level. The outside of a resting cell is positively charged with respect to the inside, but during activity permeability of the cellular membrane is increased, and the electrical characteristics of the cell are changed. The predominantly extracellular solium rushes into the cell while potassium moves out. The inrush of sodium is synchronous with depolarization of the cell while the outward flux of potassium corresponds with repolarization or with the rise in cell potential to the pre-discharge value. If the extracellular concentration of potassium is substantially increased, intracellular potassium cannot move because the concentration gradient across the membrane no longer exists, and cellular activity is paralyzed. The cell cannot recharge. The heart may be thought of as a single cell whose activity is suspended by the excess potassium in the extracellular environment. Defibrillation by potassium is effected by bringing all cells to standstill so that one pacemaker can prevail after coronary perfusion begins.

Periods of standstill from 15 minutes to one half hour are relatively safe with total body perfusion at normal temperature although some metabolism occurs even at complete cardiac standstill. An increased incidence in postoperative heart block has been reported with the use of potassium but principally by those groups employing bubble oxygenators and relatively low flow rates. Further research is being conducted regarding this circumstance.

Potassium standstill is not as safe in acquired heart disease as in congenital forms probably because of the greater frequency of pre-existing myocardial damage. The excess potassium in the extracellular compartment is simply perfused out at the conclusion of the intracardiac procedure, and heart contractions soon respond to the pacemaking area. In adults at least no fastidious effort need be made to recover all of the coronary drainage immediately after restoration of perfusion because the amount of potassium likely to enter the circulation is relatively small and ineffectual when compared with total body stores of the ion.

SUMMARY

The several forms of elective cardiac arrest which are potentially applicable to open heart surgery are: ventricular fibrillation, profound hypothermia, vagal stimulation or chemical stimulation, and potassium standstill. While some enthusiasm remains for acetylcholine and prostigmine, potassium arrest is the most commonly accepted technique.

RESUMEN

Las formas diversas de paro cardiaco electivo que se pueden aplicar a la cirugía a corazón abierto, son: la fibrilación ventricular, la hipotermia profunda, la estimulación vagal o la estimulación química y el paro con potasio. Si bien queda algún entusiasmo por la acetilcolina y por la prostignina, el paro con potasio es la técnica más comúnmente aceptada.

RESUME

Les différentes formas d'arrêt cardiaque électif qui éventuellement peuvent s'appliquer à la chirurgie à coeur ouvert, sont: la fibrillation ventriculaire, l'hypothermia grave, la stimulation pneumogastrique ou la stimulation chimique et l'immobilisation au potassuim.

Tandis que certains gardent encore leur enthousiame en faveur de l'acétylcholine et de la prostigmine, l'arrêt par le potassium est la technique la plus fréquemment acceptée.

ZUSAMMENFASSUNG

Die verschiedenen Formen des slektiven Herzstillstandes die sich als potentiell möglich bei Eingriffen am offenen Herzen anwenden lassen, bestehen in: Kammerflimmern, tiefer Hypothermie, Vagusreizung oder chemischer Reizung und Stillstand mittels Calium.

Es besteht wohl noch einige Begeisterung für das acethylcholine und das Prostigmin, doch ist der Stillstand mit Calium die häufigst angewandt Methode.

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Newer Aspects of Diagnostic and Therapeutic Management of Acute Idiopathic Pericarditis*, **

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Acute pericarditis continues to present a challenge to the clinician from the point of view of etiology and differential diagnosis as well as treatment.

Acute pericarditis occurring in the course of myocardial infarction, neoplastic diseases and advanced renal disease with uremia may be accepted as directly related to these disorders. It poses, however, an etiologic and differential diagnostic problem when it is encountered not only in the so-called idiopathic or non-specific form but even in the case of so-called rheumatic or primary tuberculous pericarditis. It has been noted by many observers f. i. how rarely isolated rheumatic pericarditis is followed by subsequent recurrence of acute rheumatic fever or any valvular defects. The diagnosis of so-called primary tuberculous pericarditis rests also usually on circumstantial evidence since bacteriological proof of tuberculosis is obtained only rarely. Clinically these three types of pericarditis resemble each other markedly. There are, however, considerable differences in treatment and also prognosis.

At times, the clinical picture of pericarditis resembles closely that of acute myocardial infarction. Whether it occurs in a middle-aged or older individual the differential diagnosis bears greatly upon the immediate and long term management.

1. *Pericarditis:* Etiologic and differential diagnostic considerations.

The dissatisfaction with the laboratory procedures currently available for this purpose have prompted a search for additional laboratory aids. Of these the fibrinogen polymerization (F.P.) test of Losner and Volk[1] held particular promise. Having noted its highly specific nature in active rheumatic fever and arthritis[2] we explored its usefulness in pericarditis and found it to be positive in a preliminary group of patients with acute rheumatic and non-specific pericarditis.[3, 4] We have since followed a total of 20 patients with pericarditis with systematic serial studies of the F.P. test as well as the conventionally used acute phase reactants including the C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), plasma fibrinogen concentration and antistreptolysin-0 (ASO) titer. In cases where myocardial infarction had to be considered we have also employed the serum GO-transaminase test.

Our experience is summarized in Table I. Some of the observations recorded here have been reported elsewhere.[5] The additional observations made since have confirmed the previous ones.

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**Presented at the 24th Annual Meeting, American College of Chest Physicians, San Francisco, June 18-22, 1959.

Methods

The procedure used for the F.P. test is a modification of the method originally reported by Losner and Volk.[1, 2] It has been described in detail elsewhere.[5] The CRP determination was carried out according to the method of Tillet and Francis and that of the erythrocyte sedimentation rate (ESR) by the method of Wintrobe and Landsberg.[7] The ASO titer was determined according to the procedure of Rantz and Randall[8] and the SGO-transaminase by the method of Karmen et al.[9] The plasma fibrinogen level was measured according to the clot density method of Losner and Volk[10, 11] which is based upon the increasing optical density of coagulating plasma.

Results

Table I summarizes the data obtained in 20 patients with pericarditis. 15 of these had non-specific pericarditis which was acute in 12 and subsiding in three. Four suffered a relapse thus permitting the observations of a total of 16 acute and four subsiding episodes of idiopathic pericarditis. Three had so-called rheumatic pericarditis, i.e. pericarditis associated with rheumatic valvular disease. Two had presumptive tuberculous pericarditis.

One of these had early constrictive pericarditis, the other hemorrhagic pericardial effusion and evidence of old apical tuberculosis. Histological examination of the pericardium removed in the first patient showed granulomatous lesions consistent with tuberculosis. In neither patient did bacteriological examination of tissue and/or pericardial fluid yield tubercle bacilli.

The initial determination of the F.P. test gave consistently positive results in the acute phase of non-specific pericarditis correlating well with the uniformly accelerated ESR and the plasma fibrinogen concentration but poorly with the CRP and the antistreptolysin-O (ASO) titer.

The F.P. test was also positive in acute rheumatic pericarditis. It correlated well with the ESR, CRP and the plasma fibrinogen concentration, but poorly with the ASO titer.

In the presumable tuberculous group the F.P. test was negative as were all other tests except the ESR.

In serial determinations extending over a period of up to 12 months

TABLE I—INCIDENCE OF ABNORMAL LABORATORY FINDINGS IN PERICARDITIS AS RELATED TO CHEST PAIN AND ACG CHANGES

Etiology	Total No. of Patients	No. of Patients With		No. of Patients with Abnormal				
		Pain	Abnormal ECG	F.P. Test	Fibr. Conc.	ESR	CRP	ASO-Titer
Non.Spec.	15	12	13	12	9	14	9	1
"Rheum"	3	3	3	3	2	2	2	0
"TB"	2	0	2	0	0	2	0	0

F.P.—Fibrinogen Polymerization
Fibr. Conc.—Plasma fibrinogen concentration (upper limit of normal 400 mgm%)
ESR—Corrected sedimentation rate
For details of patients with "Rheum." and "TB" pericarditis see text.

the F.P. test reflected closely the clinical course of idiopathic pericarditis. Similar observations were obtained in the three cases of rheumatic pricarditis of the series in agreement with our previous experiences.[2, 4]

There was also close correlation between the F.P. test and the clinical manifestations of pericarditis such as pain and between the F.P. test and the electrocardiographic changes as well. We have noted, furthermore, that the F.P. test remained positive until all clinical manifestations of activity of the disease had disappeared while the acute phase reactants usually reverted to normal at an earlier date. In several instances when the F.P. test remained positive for a prolonged period a recurrence of the acute pericarditis was observed and with it a return to abnormal of the acute phase reactants.

In contrast to the non-specific acute phase reactants the F.P. test was not affected by steroid therapy.

Of particular interest are two patients (S. R. Fig. 1, and L. R. Fig. 2 and 3) in whom a primary tuberculous pericarditis could not be ruled out entirely even though the clinical course and the laboratory findings including the F. P. test were quite consistent with the presence of nonspecific pericarditis. Since in both cases the symptoms and findings did not respond to salicylates, steroid therapy was considered. In view of the positive PPD reaction it was felt advisable to try anti-tuberculous therapy first. As seen in Figs. 1 and 2 this regimen did not prove efficacious. Temperature, symptoms and signs did not improve and the F.P. test remained positive throughout this period. When these patients were

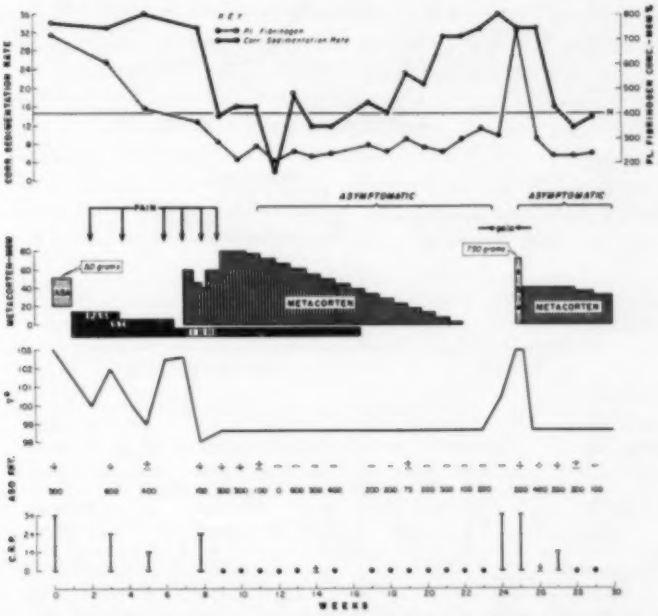

FIGURE 1: Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the ASO titer with the temperature, chest pain, and the therapy used in a patient (S. R.) with recurrent idiopathic pericarditis. (Reproduced by courtesy of American Journal of Cardiology.)

then put on steroid treatment prompt improvement of all clinical findings occurred and the F.P. test became negative.

These cases seem to confirm the value of the F.P. test as a useful aid (1) for the diagnosis of the non-specific variety of acute pericarditis, (2) for the evaluation of the continued activity of the disease, and (3) for the efficacy of treatment.

As regards so-called *rheumatic* pericarditis the doubt appears justified whether cases of isolated pericarditis even when occurring in patients with a history of rheumatic fever or presenting the findings of inactive rheumatic valvular disease are truly rheumatic in nature. Clinically this appears only certain in the presence of simultaneous rheumatic myocarditis and endocarditis or other associated major manifestations of acute rheumatic fever.

A case of pertinent interest is that of J. G. (Fig. 4) representative of the three patients of this series carrying the diagnosis of rheumatic pericarditis. This patient gave a history of repeated attacks of rheumatic fever and exhibited the residual findings of minimal mitral regurgitation. The acute episode of pericarditis for which he was hospitalized behaved in regard to the clinical course, the serial laboratory tests including the F.P. test and the response to salicylate and steroid treatment exactly like the episodes of non-specific pericarditis.

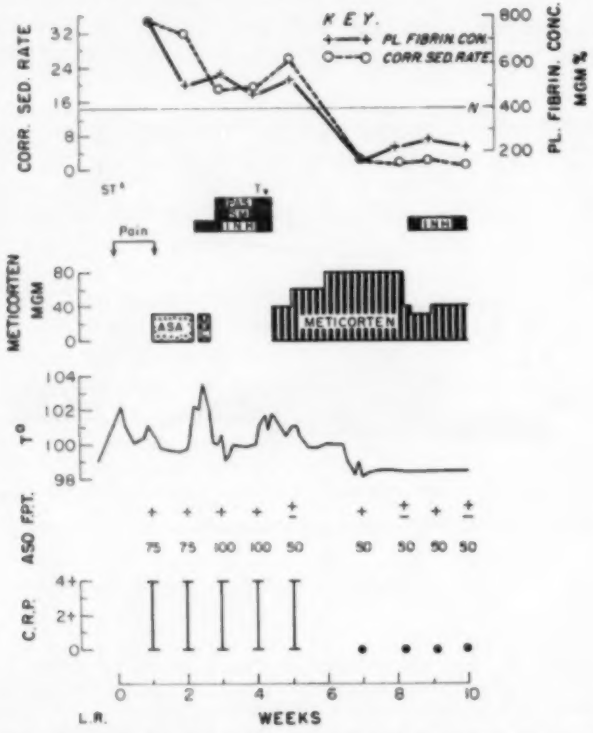

FIGURE 2: Graph demonstrating the correlation of the F.P. test, and the acute phase reactants and the ASO titer with the temperature, chest pain, and the therapy used in a patient (L. R.) with idiopathic pericarditis.

The fact that the F.P. test is positive in the acute phases of all observed cases of non-specific and rheumatic pericarditis and reflects the course of this disease as consistently as it does in active rheumatic fever with and without carditis suggests an underlying mechanism common to both conditions which interferes with the normal polymerization process of fibrinogen.

Although we have not had an opportunity to observe the F.P. test in patients with bacteriologically proved tuberculous pericarditis or pleuritis we have found the F.P. test to be negative in a patient with constrictive pericarditis in whom tuberculous granulomata with caseation were discovered in the excised pericardium. This observation suggests that a negative F.P. test may indeed help to rule out acute rheumatic or non-specific pericarditis. However, no definite conclusion as to the value of the F.P. test in tuberculous pericarditis can be drawn until this procedure can be applied to bacteriologically varified cases.

The problem of differentiation of pericarditis from *myocardial infarction* may be solved by the combined use of the F.P. test and serum enzyme determination. This problem is particularly acute when the ECG fails to show the pattern of a typical transmural infarction with abnormal Q waves or in the cases where a pericardial friction rub appears in the course of acute myocardial infarction and persists unduly long (for more than 48 hrs.). Table II lists a number of conventional phase reactants, the F.P. test and Serum enzymes (SGO-Transaminase and Aldolase) and allows a comparison of their behaviour in non-specific pericarditis and myocardial infarction. It is evident that where differentiation is usually most difficult—that is between subacute pericarditis and atypical myocardial infarction—the combined determination of the F.P. test and of the serum enzyme levels constitutes a particularly useful laboratory aid.

In the occasional patient who develops an acute pericarditis superimposed upon a recent myocardial infarction—Dressler's post-infarction syndrome[12] the utilization of the F.P. test in combination with the SGO-transaminase test should be helpful in the differential diagnosis since this syndrome has been related to non-specific pericarditis. Unfortunately the patients in whom we suspected this condition on clinical grounds were all on anti-

TABLE II—THE DIFFERENTIAL DIAGNOSIS VALUE OF VARIOUS LABORATORY FINDINGS IN MYOCARDIAL INFARCTION AND PERICARDITIS

Laboratory Data	Acute Myocardial Infarction		Pericarditis	
	Transmural	Atypical	Acute	Subacute
E.S.R.	frequ. elevated	frequ. normal	elevated	frequ. elevated
C.R.P.	usually elevated	frequ. normal	frequ. elevated	frequ. normal
Fibr. Conc.	usually elevated	frequ. normal	frequ. elevated	frequ. normal
F.P.	negative	negative	positive	positive
S. Enz.	elevated	frequ. normal	normal	normal
Q	abnormal	usually normal	normal	normal
Ekg. ST	frequ. elevated	norm., depr. or elev.	frequ. elevated	normal
T	prog. inverted	frequ. inverted	may be inverted	may be inverted

F.P.—Fibrinogen Polymerization
Fibr. Conc.—Plasma Fibrinogen Concentration
S. Enz.—Serum Enzyme Level (SGO—Transaminase or S. Aldolase)

coagulant therapy. The resultant prolongation of prothrombin and clotting time makes it impossible to carry out the F.P. test since it prolongs the procedure beyond practical limits of time (often beyond eight hrs.).

2. *Treatment of acute pericarditis.*

a) Non-specific pericarditis.

The treatment of this condition is difficult to evaluate in many cases of mild to moderate degree in view of the self-limiting nature of the disease. Equivocal results have been reported not only with salicylates but also with a number of antibiotics including penicillin, streptomycin, achromycin, terramycin, alone or in combination. In more severe cases characterized by prolonged chest pain, a protracted febrile course and persistent pericardial effusion we have found the prompt administration of steroids most efficacious. This confirms the isolated reports by others.[13-15] Very large doses may have to be used, occasionally as high as 80 mgm of prednisone daily. Steroid therapy does not necessarily prevent recurrences but it is equally effective, usually in smaller dosage, when these set in. The prolonged and relapse-prone course of non-specific pericarditis noted in some of our patients afforded us a particular opportunity to observe the effect of steroid therapy not only upon the clinical course but also upon the serial laboratory tests (Figs. 1 and 2).

The institution of this regimen leads to prompt improvement of the symptoms and normalization of the temperature usually in 24 to 48 hours. Within a short period the acute phase reactants return also to normal. The F.P. test, however, remains positive for a longer period. To discontinue steroids at this point—or even to reduce the dosage gradually—in the belief that the disease process has been already materially affected leads, however, to a quick relapse. This is well indicated not only by the prompt return of the temperature but also of chest pain and even physical signs. Only when the F.P. test has turned negative and has remained so for at least two weeks is it advisable to reduce the steroids in the manner usually

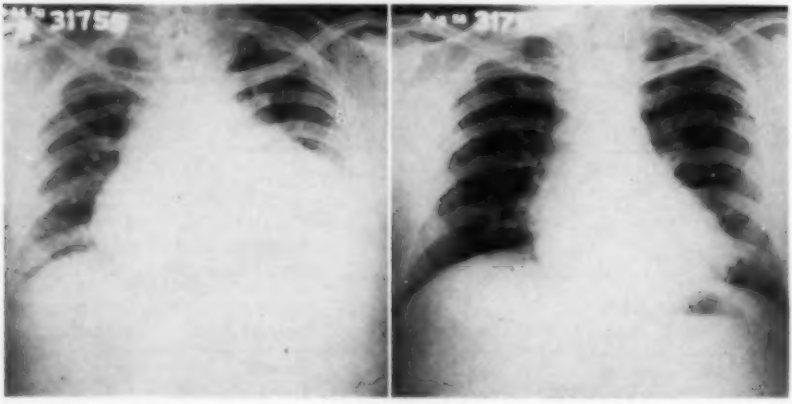

FIGURE 3A FIGURE 3B

Figure 3A: Cardiac silhouette before steroid therapy shows increase in size and abnormal configuration due to massive pericardial effusion.—*Figure 3B:* Cardiac silhouette 2 weeks after institution of steroid therapy.

recommended for a high dosage regimen. The F.P. test thus furnishes guidance for the management of this disease. When relapses occur following eventual discontinuation of steroids both the acute phase reactants and the F.P. test become positive again. The latter will serve again as the more valuable guide for the therapeutic regimen. It should be pointed out that patients may be ambulated and even returned to moderate activity as soon as the steroids have exerted their full effect.

b) *Rheumatic Pericarditis*

Our observations on the treatment of so-called rheumatic pericarditis confirm the adequacy of salicylate therapy in most cases as noted by others. Steroid administration may be required in patients intolerant of salicylates and/or suffering from a more severe form of this disease. Our experience again supports the value of the F.P. test as a reliable guide to the efficacy of therapy in rheumatic pericarditis (J. G. G. Fig. 4).

c) *Tuberculous Pericarditis*

In cases where tuberculous etiology cannot be ruled out with certainty the advisability of steroid therapy may be questioned. However, it has been used with success not only in pleurisy of probable or proved tuberculous nature [16, 17] but also in proved tuberculosis pericarditis.[16, 17] Voegtlin[17] reported on the excellent response of tuberculous pericarditis with massive effusion and tamponade to cortisone after triple anti-tuberculous therapy had failed to halt the rapid reaccumulation of pericardial and pleural fluid. The effusions disappeared within eight days of cortisone administration. No pulmonary parenchymal lesion appeared. The cortisone treatment did not prevent the early onset of constrictive pericarditis in one patient.

While primary tuberculous pericarditis, that is without obvious concomitant lesions elsewhere is quite rare, the prophylactic use of isoniazid (INH) is advisable in cases of non-specific pericarditis where there is

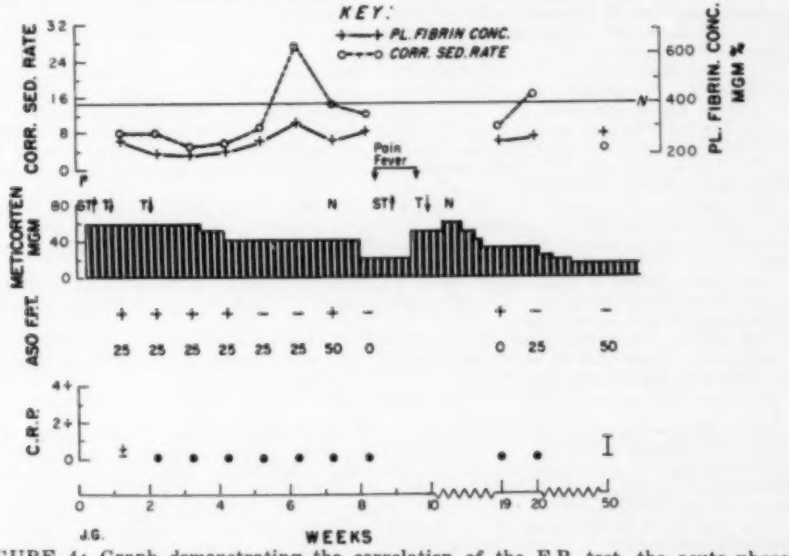

FIGURE 4: Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the ASO titer with the chest pain, and the therapy used in a patient (J. G.) with rheumatic pericarditis.

reasonable suspicion of a tuberculous cause. This was done in two our patients. One of these (S.R.) (Fig. 1) suffered numerous recurrences following the first episode which occurred during war imprisonment. The other (L.R. (Fig. 2) had mild to moderate symptoms but persistent massive hemorrhagic pericardial effusion. Both had a second strength positive PPD reaction. However, the temperature, symptoms and signs did not respond to antituberculous treatment. All findings, clinical and laboratory cleared promptly after prednisone treatment was started. Prolonged follow-up observations failed to reveal evidence of tuberculosis. Thus both cases could be considered to have non-specific rather than tuberculous pericarditis.

SUMMARY

Comparative serial studies of the fibrinogen polymerization test, with several acute phase reactants such as the C-reactive protein, the erythrocyte sedimentation rate and plasma fibrinogen concentration, and also the antistreptolysin-O titer were carried out to explore their relative usefulness, for the differential diagnosis of non-specific rheumatic and tuberculous pericarditis.

A consistently positive F.P. test indicated the presence, and mirrored the course, of rheumatic and idiopathic pericarditis, while it was negative in tuberculous pericarditis. Of the acute phase reactants only the ESR was abnormal to a comparable degree in all conditions studied. It seems, therefore, that the F.P. test can serve as a valuable aid in the diagnosis of idiopathic pericarditis.

The F.P. test appears, furthermore, of value for the differential diagnosis between atypical myocardial infarction and acute nonspecific pericarditis, particularly, when used concomitantly with the serum GO-transaminase or aldolase tests.

The treatment of pericarditis is discussed and the value of steroid therapy in nonspecific and rheumatic pericarditis of severe degree is emphasized.

The F.P. test provides a particularly useful criterion for the efficacy of therapy since it appears not to be suppressed by salicylate or steroid therapy and reflects the activity of the disease.

RESUMEN

Se ha llevado a cabo una serie de estudios comparativos de la prueba de la polimerización del fibrinógeno con varios reactivantes de fase activa tales como el reactivo C de proteina; también se estudió la sedimentación de los eritrocitos, la concentración de los eritrocitos, la concentración en el plasma del fibrinógeno, saí como el título de la antiestreptolisina-O esto se ha hecho con el objeto de averiguar su relativa utilidad, para el diagnóstico diferencial de la pericarditis no específica reumática y de la pericarditis tuberculosa.

Una polimerización del fibrinógeno (FP) persistentemente positiva refleja la evolución de la pericarditis reumática e idiopática en tanto que cuando es tuberculosa la prueba FP es negativa.

De los reactivantes en fase aguda, sólo la velocidad de la sedimentación globular fué anormal en grado comparable entodos los padecimientos estudiados. Parece por tanto, cue la reacción FP puede servir como una ayuda de valor para el diagnóstico de la pericarditis idiopática.

La reacción FP parece además, ser de valor para el diagnóstico diferencial entre el infarto atípico del miocardio y la pericarditis aguda no específica en particular cuando se usa al mismo tiempo con las pruebas de transaminasa GP o aldolasa en el suero.

Se diserta sobre el tratamiento de la pericarditis y sobre el valor de los esteroides en el tratamiento de la pericarditis no específicas y reumáticas y de grave evolución, siendo esto lo que se recalca.

La prueba FP proporciona un criterio de utilidad para la eficacia del tratamiento puesto que parece que no se suprime por el uso de salicilatos o esteroides y refleja la actividad de la enfermedad.

RESUME

Une série d'études comparatives du te de la polymérisation du fibrinogène avec plusieurs réactions des processus aigus tels que la protéine réactive C, le taux de sédimentation de l'érythrocyte, la concentration plasmatique fibrinogène, et aussi le titre antistreptolysine O, furent poursuivies pour explorer leur utilité relative, dans le diagnostic différentiel des péricardites rhumatismales, non-spécifique, et tuberculeuse.

Un test de la polymérisation du fibrinogène nettement positif indiquait la présence et reflétait l'évolution d'une péricardite rhumatismale et idiopathique, tandis qu'il était négatif dans la péricardite tuberculeuse. Sur les réactions des processus aigus, seul le taux de sédimentation érythrocytaire fut anormal à un degré comparable dans tous les états étudiés. Il semble alors que le test de la polymérisation du fibrinogène

puisse servir comme un moyen appréciable dans le diagnostic de la péricardite idiopatique.

Le test de la polymérisation du fibrinogène apparait, ensuite, valable pour le diagnostic différentiel entre l'infarctus myocardique atypique et la péricardite aiguë non spécifique, particulièrement quand il est utilisé en même temps que les tests de l'aldolase ou de la transaminase du sérum.

Le traitement de la pédicardite est discuté, et l'auteur souligne la valeur de la corticothérapie dans les péricardites non-spécifique et rhumatismale graves.

Le test de la polymérisation du fibrinogène fournit un critère particulièrement utile pour apprécier l'efficacité du traitement depuis qu'il semble ne pas être supprimé par le traitement salicylé ou par les stéroïdes, et reflète l'activité de l'affection.

ZUSAMMENFASSUNG

Es wurden vergleichende Reihenuntersuchungen des Fibrinogen-Polymerization-Testes (F.P.) durchgeführt mit verschiedenen rasch verlaufenden Reaktionen wie z.B. dem C-empfindlichen Protein, der Blutsenkung, der Plasma-Fibrinogen-Konzentration und auch dem Antistreptolysin-Titer zur Erklärung des relativen Wertes bei der Differentialdiagnose von unspecifischen rheumatischen und tuberkulösen Pericarditiden.

Ein übereinstimmend positiver F.P.-Test zeigt, das Vorliegen und spiegelt den Verlauf einer rheumatischen und idiopathischen Pericarditis, wohin gegen der negativ ausfiel bei tuberkulöser Pericarditis. Von den rasch verlaufenden Reaktionen war nur die BSG in vergleichbarem Grade in allen untersuchten Fällen verändert. Es scheint daher, als könne der F.P.-Test als ein wertvolles Hilfsmittel gelten bei der Erkennung der idiopathischen Pericarditis.

Der F.P.-Test scheint darüber hinaus von Bedeutung für die Differentialdiagnose zwischen atypischen Myocardinfarkten und akuter unspezifischer Pericarditis, besonders wenn er zusammen mit dem Serum-GP-Transaminase-Test (Aldolase-Test) gebraucht wird.

Es wird die Behandlung der Pericarditis besprochen und der Wert der Steroid-Therapie bei unspezifischer und rheumatischer Pericarditis von ziemlicher Schwere betont.

Der F.P.-Test liefert ein besonders nützliches Kriterium für die Wirksamkeit der Therapie, da er augenscheinlich nicht beeinträchtigt wird durch Salicylate oder Steroid-Therapie und die Aktivität der Erkrankung wieder gibt.

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ELECTROCARDIOGRAM OF THE MONTH

Possible Thiamine Deficiency

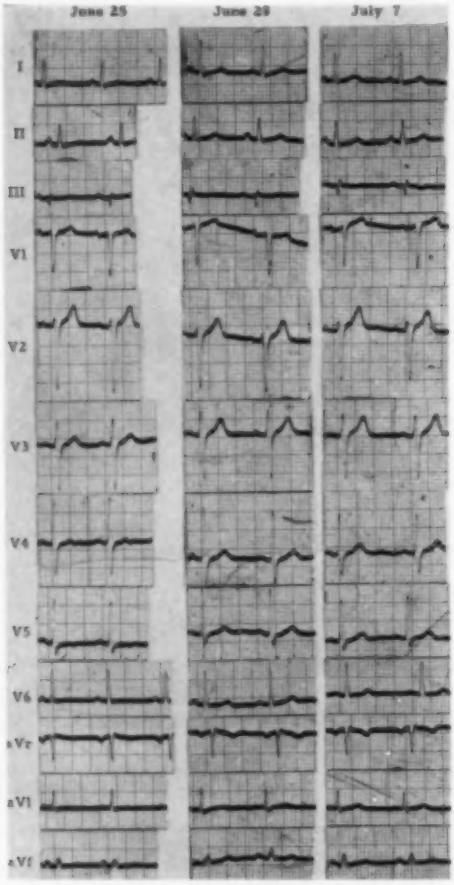
L. F., a 49 year old white man, was examined for acute midepigastric distress on June 25, 1958.

Physical examination was negative, with no evidence of systemic disease. Fluoroscopy, too, was normal.

He conceded to poor eating habits and excessive drinking during the last two weeks.

The electrocardiogram taken on June 25th was considered definitely abnormal. There was a regular sinus rhythm; the P-R interval was at the lowermost limit of normal (0.12 second) in several leads. The T-wave was almost isoelectric in leads I and II. Lead III shows low voltage of the QRS complex. The chest leads show inversion of the T-wave in V5 and flattening in V6. These changes were felt to be non-specific and non-diagnostic. The combination of these findings, however, suggested the possibility (if not probability) of thiamine deficiency.

He was given 200 mg. of thiamine chloride in combination with other B-complex components on June 26 and again on June 27.



A second electrocardiogram on June 28 showed remarkable reversion to near normal. A third record taken on July 7 may certainly be considered normal.

In view of the fact that the patient was deemed clinically not to be suffering from coronary artery disease, and that the electrocardiogram had returned to normal after treatment of an extracardiac condition, a two-step (Master) test was performed (carefully prepared and supervised, of course). It was unequivocally normal. Five months after his last treatment there was no detectable sign or symptom of coronary artery disease, and he was entirely symptom-free; the ECG was normal on November 6, 1958.

Non-specific or non-diagnostic findings in an electrocardiogram have often been overzealously interpreted as positive evidence of coronary artery disease. With increasing knowledge and greater experience it is now appreciated that a host of conditions unrelated to heart disease may cause patterns similar or identical to "coronary" patterns (e.g. position, electrolytic changes, hormone deficiency, etc.). This has lead many to the opposite extreme, so that they become evasive to a point where an otherwise valuable test may be rendered meaningless. As much as it behooves the physician to make an attempt to find a specific cause for such non-specific features (e.g. fever, anemia, hypertension), so an effort should be made to define the specific nature of a non-diagnostic abnormality in the electrocardiogram. This is often impossible, of course, but it may be rewarding to all concerned if in his report the interpreter would state that the observed changes, although non-diagnostic, may be seen in association with certain conditions. The latter may then be enumerated.

In our case we found low voltage, low T-waves, a short P-R interval and slight S-T displacement. Such a pattern suggested thiamine deciency as described, among others, by Scherf.

This was not stated as more than a mere suggestion and could not be considered a definite diagnosis. We believe, nevertheless, that the clinical history and prompt response demonstrated that the electrocardiogram was an invaluable aid in this instance.

On the basis of the ECG alone one could not rule out the existence of a small or subendocardial infarct. The clinical data favor an extracardiac explanation for the T changes. Thiamine deficiency seems to be the most likely and logical cause. It must be conceded, however, that positive proof cannot be offered.

This case is presented first as a reminder of the existence of this condition. Secondly, it is offered to permit consideration of the terms "non-specific" and "non-diagnostic" in an electrocardiographic interpretation as a challenge which one should try to meet without complacency.

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X-RAY FILM OF THE MONTH

Clinical Information

Colored female, age 31, admitted Feb. 1, 1958, with slight cough and left chest pain. Chest film on Feb. 3 is shown below. She had used plastic hair spray three times a week over a period of three years. Laboratory studies were normal. Sputum was negative and skin tests for fungus were negative. The P.P.D. was positive. A scalene node was normal on biopsy. Lung biopsy March 4 was interpreted as "Loeffler's pneumonitis." It was felt that inhalation of the hair spray could not produce this pathological picture.[1] The patient improved clinically and the roentgen signs regressed about 50 per cent. In May, a roentgenogram showed considerable progression of the pulmonary lesions.

ANSWER

A second lung biopsy was diagnosed as collagen disease, probably periarteritis nodosa. The large ill-defined nodules disseminated through the lung fields are not diagnostic of periarteritis but are encountered in this condition. The eosinophils noted on the first lung biopsy were not seen on the second biopsy made two months later. The findings on the biopsy plus the disseminated and progressive lesions in the lung should suggest the possibility of periarteritis.[2] It is conceivable that the patient may ultimately prove to have Wegener's syndrome or allergic angiitis and granulomatosis.[3, 4]

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Esophageal Obstruction Caused by Vascular Anomaly

A Case Report

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Surgical significance of anomalies of the bronchial arteries are not well recognized. Little has been written concerning the subject other than cadaver studies and anatomic reviews.[1-2] The case reported, shows an occurrence of this anomaly in 0.6 per cent of postmortem studies. Search of the literature fails to reveal a reported case of bronchial artery anomalies producing clinical symptoms.

In May 1955, a 32 year old woman with a 12 year history of intermittent esophageal obstruction characterized by dysphagia, regurgitation, choking on meat, occasional excessive saliva and substernal pain. She managed to avoid these symptoms by restricting her diet to liquids or "just not eating." As her symptoms would subside she would gradually return to a diet of semi-solid foods. She was given trials of medications during this 12 year period with only temporary results.

In May 1955, a barium swallow was done, revealing an extrinsic esophageal constricting lesion at the level of the eighth dorsal vertebra.

Esophagoscopy showed the obstructive lesion 32 cm. from the upper gum margin. Esophagitis was present at the obstructive site and the lumen was of pencil point diameter.

At thoracotomy, two abnormal vessels arose from the left bronchial artery and passed anterior to the esophagus over its surface at the level of constriction. These vessels were ligated and divided. An esophagoplasty was done at the stricture area.

Postoperatively, a Levine tube was left in place for 11 days, then removed. Bilateral pneumothorax was treated with intercostal catheters and under water seal drainage. Antibiotic therapy was carried on through the entire postoperative course. She was discharged on the 15th postoperative day.

At five and one half weeks, postoperative esophageal dilation was begun with web-woven bougie Number 24. She was dilated at weekly intervals, graduating to a Number 42 bougie in six and one half weeks. Dilation at bimonthly intervals was continued for six months with Number 38 and 42 bougies. All dilations were accomplished with ease and she ate solid foods for the first time eight weeks postoperatively without difficulty. Fifteen month follow-up examination revealed clear lung fields. A Number 42 bougie passed with ease and she ate a regular diet without symptoms. She gained approximately 11 pounds in the year following operation.

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Report of the Committee on Microbiology

American College of Chest Physicians

The various items discussed and proposed for adoption are as follows:

I. *The Classification of Significant Acid-Fast Bacilli That Produce Disease in Man*

A. The whole field of acid-fast bacteria was divided into two convenient groups for purposes of identification and separation. A third group is added where acid-fast forms may interfere in identifying pathogenic forms.

(1) Typical. True tubercle bacilli—M. tuberculosis—var. hominis.

(2) Atypical. Other pathogenic bacilli infecting human beings.

(a) Of human origin
1. Leukoflavin
2. Battey
3. Scrofulaceum (luteum)
4. Fortuitum
5. Ulcerans
6. Balnei
7. Leprae
8. Kansasii

(b) Of animal origin
1. M. tuberculosis var-bovis
2. M. avium

(3) Acid-fast bacteria and other forms and objects other than mycobacteria that may be confused with mycobacteria pathogenic for man.

(a) 1. Some actinomyces
2. Nocardia
3. Artefacts—Certain spores, fat or wax covered bacilli, etc.

(b) Poikiliothermic mycobacteria—many strains found in cold-blooded animals.

(c) Saprophytes
1. Slow growing (pigmented and non-pigmented)
2. Rapidly growing (pigmented and non-pigmented)

B. Means of Identification and Study

(1) Morphology
(a) Microscopic appearance
(b) Colonial morphology

(2) Physiologic Methods
(a) Growth requirements—culture media
(b) Metabolic activity
(c) Bacterial resistance
(d) Pigment production

(3) Chemical Methods
  (a) Enzymatic
    1. Niacin—Kono's test
    2. Oxidation—reduction
    3. Arylsulphatase activity
    4. Catalase
    5. Peridoxidase
    6. Neutral red reaction
(4) Immunological
  (a) Antigenic—skin reactions
  (b) Antibodies
    1. Agar diffusion
    2. Electrophoresis.
(5) Animal pathogenicity for
  (a) guinea pigs, rabbits, rats, mice, hamsters, monkeys, birds, calves.
  (b) Embryonated eggs.

II. *Standard Methods for Testing Resistance*

Methods for both direct and indirect antimicrobial susceptibility determinations are outlined in detail in brochures prepared by the Veterans Administration (T. B. Laboratory Methods), the Trudeau Laboratory (Routine Procedures used at the Trudeau Laboratory), and numerous published reports. (Also see Egons Darzin's textbook, *Bacteriology of Tuberculosis*, University of Minnesota Press, 1958.)

III. *Methods for Testing Virulence of Mycobacterium Tuberculosis*

A. Differentiation of mycobacteria from the standpoint of pathogenicity is often extremely difficult. This is due to the necessity of qualifying the term "virulence" on the basis of strain characteristics, infective dose, route of inoculation, nutritional state of the animal, species susceptibility or resistance, time interval between infection and disease, and all other factors which must be considered. While animal testing is one of the most reliable methods available for evaluating the pathogenic potentialities of tubercle bacilli and other mycobacteria, it must not be forgotten that pathogenicity for the animal may differ from that for man.

B. In view of the limitations of the animal virulence test, efforts have been made to recognize other criteria for virulence. A number of procedures have been developed which have proved of great help.

Some of the more useful tests are as follows:

1. Morphology (Cord formation as described by Middlebrook and Dubos)
2. Neutral red test
3. Oxidation-reduction, catalase, peroxidase, etc.

IV. *Possibilities of Bacteriophage Against Tuberculosis*

A. Bacteriophages are available against all mammalian tubercle

bacilli and against most of the other mycobacterial species except *M. Avium* and *M. Battey.*

B. They have possibilities for identifying and classifying mycobacteria as well as in studying their chemical and microbiological characteristics.

V. *Methods for Diagnosing Common Fungus Disease*

A. Antigens are commercially available for blastomycosis, coccidioidomycosis, and histoplasmosis, the specifications in preparation of which are similar to those of tuberculosis. Tests for other fungi are being studied but reliable antigens are not generally available.

B. Standardized preparations of histoplasmin and coccidioidomycin, recommended by the National Institute of Health, Division of Biological Standards, should be employed freely in testing with fungus antigens for any lesions, especially those where tubercle bacilli cannot be isolated.

C. Cultural—In general, the cultural procedures are similar for the systemic mycoses with the exception of the *Actinomyces*, which are anaerobic. It is preferable to use both Sabouraud's or potato dextrose agar and blood agar. The plates are inoculated with about 1 cc. of sputum each, and spread evenly over the plates. The sputum is not digested. The media should contain 40 units of streptomycin and 20 units of penicillin per cc. One plate of each type of media is incubated at 37° C. and one plate at room tempearture. *Candida albicans* can be expected to grow in 48 hours, *Coccidioides* in about 7 to 10 days, and *Histoplasma* in about 10 to 14 days. However, none of the plates should be discarded in less than a month, since sometimes some of the organisms are extremely slow growing. (The great danger of inhalation infection of laboratory personnel when handling coccidioidomycosis and histoplasmosis organisms make completely closed technics mandatory.)

D. Serological—The serological tests for the fungus diseases are extremely valuable in coccidioidomycosis, histoplasmosis and blastomycosis. There are no standardized published tests for the other systemic mycoses. The serological tests for the three above-named mycoses may be performed either by complement fixation with several antigens or by precipitin or by red cell or collodion absorption of the specific testing material followed by agglutination. Ground yeast phase organisms are also employed in the tests. The procedure most commonly employed is the complement fixation test using either the mycelial or yeast phase antigens. The test is positive only during the acute stages of the disease and furnishes very reliable information, not only about diagnosis, but prognosis, providing repeated tests are secured. A continually high titer or a rising titer suggests a poor prognosis. It must be stated that up to 20 per cent of proved cases of mycotic infection show no serological response and possibly as many as this show no skin test response. They should not, therefore,

be regarded as 100 per cent exclusion tests. (These tests should only be done by experienced laboratory personnel. They can be performed by the U. S. Public Health Service on specimens sent through State Health Department Laboratories.)

E. Animal Inoculation—Mouse inoculation may be useful as a supplementary procedure to culture, but is not absolutely essential.

F. Pathology—The pathology of mycotic infections is quite variable but in general the pathology is like other chronic infections, after a variable period of the acute onset of the disease. Most of the pathology is described in standard texts on mycotic infections.

G. Staining—The staining methods most helpful may be listed in order of usefulness as follows:

1. Gomori's Methenamine silver stain for fungi especially histoplasmosis, but is also useful for most other fungus spores and mycelia.
2. Gridley's special stain.
3. PAS Stain, including Hotchkiss-McManus Stain.
4. Mucicarmine is the stain of choice to show the capsules of *Cryptococcus neoformans.*

VI. *Staphylococci*

A. When mycobacteria are not found, search should be made for other pathogenic micro-organisms, especially staphylococci, streptococci, Klebsiella, and Pseudomonas strains, as well as certain gram negative bacilli and even anaerobic forms.

B. Pathogenic and suspected pathogenic staphylococci should be tested for any resistance as a guide to treatment. Phage typing should be used for epidemiological studies.

VII. *Viral Infections*

A. Great progress has been made in the investigation of viral infections. Laboratory diagnosis is based upon isolation of the virus from clinical specimens or by demonstrations of significant rise of antibodies between the acute and convalescent serum samples.

B. Diseases such as psittacossis, Q fever, and influenza are most readily confirmed by the complement fixation test. In primary atypical pneumonia patients will show an increase in the titer of cold agglutinins during convalescence.

C. The virus of influenza A, B, and C may be isolated by inoculation of throat washings into the amniotic sac of chick embryos. The hemagglutination inhibition antibodies may also be demonstrated in the acute and convalescent sera. A number of newer respiratory viruses have been discovered by use of suckling mice and, more recently, by use of tissue cultures.

D. The Group A Coxsackie viruses which may be isolated by inocu-

lation of throat washings into suckling mice are important as causative agents of herpangina. The Group B, Coxsackie viruses, which are most readily isolated by inoculation of throat washings or feces into monkey kidney tissue cultures, have been shown to be important agents of epidemic pleurodynia or Bornholm disease.

E. A large group of viruses designated as APC or adenoviruses have been found by Heubner, *et al* in association with various respiratory infections. Some of these agents, particularly adenovirus type 4, may cause illness resembling primary atypical pneumonia. Adenovirus infections may be confirmed by inoculation of throat washings into "Hela" cell tissue cultures or by demonstration of CF or neutralizing bodies in acute and convalescent sera. Other respiratory viral agents that have been recently discovered by the use of tissue culture methods are the so-called hemoagglutination adsorption agents, JG agents of Price, and ECHO virus type 20.

VIII. *Parasitology*

Owing to the fact that there was a full agenda and that many places require search for animal parasites in sputum, tissues, and chest fluid, your committee is taking up this subject in more detail at a later time and will make a report at the next meeting.

COMMITTEE ON MICROBIOLOGY
AMERICAN COLLEGE OF CHEST PHYSICIANS

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The President's Page

AESCULAPIUS AND THE MUSES

One of the astonishing things in the history of medicine is the transience of medical glory. The achievements of Western medicine have surely been woven on one loom; the fabric is continuous at least since before the great days of Pauda in the fifteenth century and perhaps before the fabled days of Salerno, when Sicilian medicine was regarded as magic by medieval Europe. But within the boundaries of Europe and the near East, within this homogeneous development, progress has been most unpredictable. Over and over again the mecca of one generation of medical students has become just another medical school to the next, as preeminence in medicine has darted hummingbird fashion from one school, one country, to another.

But perhaps medical greatness is not so much a matter of chance as a superficial view of medical history would suggest. A shrewd observer speculating on the medical scene about the middle of the last century could perhaps have predicted the coming strength of German medicine, and twenty-five years later he might have foreseen the rise of Vienna and then the American medical centers. For progress in medicine has always had two roots; on the one hand it has arisen out of the common tradition available to all, but on the other it has arisen out of a local intellectual ferment. One could have predicted the rise of German medicine in the nineteenth century by reason of the preeminence of German culture—its literature, its music, its philosophy. The fact is, a great medicine is a concomitant of a great culture, and cannot long survive the demise of that culture.

Nor is the relationship between culture and medicine so very mysterious. Every major advance in medicine depends upon the opening up of some new vein of research. An individual or a school learns to look at old problems in a new way, and discovery follows discovery. But sooner or later the new approach becomes less fruitful, since every way of looking is limited and partial. The greatest discoveries in medicine sooner or later become blind allies; they can even become positive impediments. Hence continued progress depends upon the ability to remain always fresh in one's approach to problems, always willing to re-examine the old orthodoxies. Progress is a product of speculation.

What history tells us is that the intellectual energy and open-mindedness necessary for speculation have their roots outside of medicine. These qualities must pervade the whole intellectual community. The same energy which produces great art and great philosophy produces great medicine.

This is of course just a variation of the old truism of interdependency: No man is an island, nor dare any branch of knowledge assume its independence of other branches. But it is a particularly appropriate truism for medicine today. Never in history has the prestige of the physician been higher, and if trustees and legislators at times prove recalcitrant in specific instances, it is nevertheless true that they are fabulously open-handed to medical schools and foundations in comparison with their attitude toward other branches of knowledge. This constitutes an invitation to "go it alone," to accept the largesse newly available, and to neglect the cause of the other branches of learning. And some medical centers, particularly, seem willing to accept the invitation.

But the stretch to greatness must be a cooperative effort. You cannot build a great medical school by a handsome new plant at the edge of the campus if torpor prevails around the oval. History is luminously clear in this matter. The medical profession cannot concern itself merely with medical education; it must use its immense prestige on behalf of education generally.

Seymour M. Farber

ALBUQUERQUE MEETING SCHEDULED FOR SPECIAL TV PROGRAM

The Silver Anniversary Homecoming Meeting of the American College of Chest Physicians has been selected for the MEDICAL SPECIAL EVENTS TV Series presented by The Upjohn Company. These telecasts are produced and moderated by TV commentator and author, Howard Whitman. Previous telecasts in the series have dealt with heart disease, cancer, occupational medicine, air and space medicine, plastic surgery, and mental health, each produced in cooperation with a major medical society.

A one-hour live telecast on CANCER OF THE LUNG will be presented in cooperation with the American College of Chest Physicians during the Albuquerque meeting, October 14-17. It will be telecast live in Albuquerque and video-taped for later national broadcast.

Chapter News

COLORADO CHAPTER

The Colorado Chapter will present a Postgraduate Course on Cardiopulmonary Diseases in Denver, October 30 and 31, in co-sponsorship with the Colorado Heart Study Club, Fitzsimons Army Hospital, the National Jewish Hospital and the University of Colorado School of Medicine. The tuition fee is $20, but will be waived for members of the chapter and the Colorado Heart Study Club. Following is the program:

October 30—National Jewish Hospital

9:00 a.m. Panel discussion: "Cardiopulmonary Effects of Air Pollution and Tobacco Smoke"
Moderator: Roger S. Mitchell, Denver
Panel: Gardner Middlebrook, Denver; Hurley L. Motley, Los Angeles; Richard A. Prindle, Washington, D.C.; Richard Reece, Denver

12:15 p.m. Business meeting, Colorado Chapter

12:30 p.m. Luncheon
Sabin Auditorium, University of Colorado Medical Center

2:00 p.m. Panel discussion: "Dyspnea"
Moderator: Murray Hoffman, Denver
Panel: Samuel Bukantz, Clayton, Missouri; George C. Griffith, Los Angeles; Solbert Permutt, Baltimore; George Wilcox, III, Denver

6:30 p.m. Dinner meeting (Colorado Heart Study Club, University Club)
George C. Griffith, Los Angeles, guest speaker

October 31—Fitzsimons Army Hospital

9:00 a.m. Clinical session with case presentations
Moderator: Colonel James A. Wier, Denver

INDIANA CHAPTER

The Indiana Chapter will have a luncheon meeting at the Athenaeum Turner's Club in Indianapolis, October 7. Dr. John Hickam, Indianapolis, will speak on "Management of Cor Pulmonale."

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter will meet at the Penn Sheraton Hotel, Philadelphia, October 20, in connection with the 109th Annual Session of the Medical Society of the State of Pennsylvania. The following program will be presented:

3:30 p.m. Panel discussion: "Management of Chronic Bronchitis and Emphysema"
Moderator: Katharine R. Boucot, Philadelphia
Panel: Albert H. Andrews, Chicago (inhalation therapy)
Louis R. Davidson, New York City (surgical aspects, including tracheal fenestration)
Jack D. Myers, Pittsburgh (cardiovascular aspects)
Frances J. Sweeney, Philadelphia (antibiotic therapy)

POTOMAC CHAPTER

The annual meeting of the Potomac Chapter will be held at the Greenbrier Hotel, White Sulphur Springs, West Virginia, October 9. The program is as follows:

9:00 a.m. Registration

9:30 a.m. Moderator: W. L. Cooke, Charleston, West Virginia, Chapter President

"Tobacco and Cancer"
Robert C. Hockett, New York City

"Air Pollution"
Peter V. Hamill, Washington, D. C.

"The Pneumoconioses—Diagnosis and Management"
Frank Princi, Cincinnati, Ohio

"X-ray Diagnosis of Diffuse Pulmonary Pathology Proven by Lung Biopsy"
Mark Wholey, Charleston, West Virginia

11:50 a.m. Business meeting

12:30 p.m. Luncheon

2:00 p.m. Moderator: Milton B. Kress, Baltimore, Chapter Vice President

"Coccidioidomycosis"
James H. Matthews, Oteen, North Carolina

"Blastomycosis"
Harry E. Walkup, Oteen, North Carolina

"Histoplasmosis"
Timothy Takaro, Oteen, North Carolina

"Present Status of the Drugs Used Less Frequently in Tuberculosis"
James H. Matthews, Oteen, North Carolina

"Open Heart Surgery"
R. Adams Cowley, Baltimore

JAPANESE CHAPTER

Members of the Japanese Chapter arranged a special meeting in Tokyo on June 9 in honor of the visit of Dr. and Mrs. Richard H. Overholt, Boston. Dr. Overholt spoke on "The Present Status of Thoracic Surgery."

CANARY ISLANDS CHAPTER OF SPAIN

The Canary Islands Chapter held its spring meeting in Santa Cruz de la Palma, May 22-24, under the direction of Dr. Tomás, Cervía, Governor for the College. The meeting was opened on May 22 by the Mayor of Santa Cruz de la Palma who greeted members and guests. An exhibit and panel discussion on cardiorespiratory function were presented. Dr. del Arco Montesinos of Santa Cruz served as moderator, with Drs. A. Bosch Millares, Las Palmas, E. Gonzalez, La Laguna, and Mendes de Lugo of Santa Cruz as panelists. A second panel discussion on congenital bronchopneumonopathy was presented on May 23 which was moderated by Dr. Tomás Cervía. Drs. M. Cuesta Palomero, Puerto de la Cruz, M. García González, D. Ponce Arencibia and F. Pérez Pérez of Las Palmas, and P. Rodríguez Trijilli and R. Capote of Santa Cruz de Tenerife served as panelists. Following the scientific sessions, those attending the meeting toured the island and were received by the mayors of various cities.

TURKISH CHAPTER

The Turkish Chapter held its annual meeting in Ankara in June. Panel discussions on bronchial asthma, moderated by Dr. Tevfik Saglam of Istanbul, and on cor pulmonale with Dr. Celal Ertug of Ankara as moderator, were presented. The following officers were elected:

President:	Ihsan Rifat Sabar, Istanbul
Vice-President:	Tevfik Ismail Gokce, Istanbul
Secretary-Treasurer:	Celal Ertug, Ankara (re-elected)

NEWS NOTE

Dr. Anton Sattler, Vienna, Austria, Regent of the College for Austria and Secretary-General of the Sixth International Congress on Diseases of the Chest to be held in Vienna, August 28-September 1, 1960, addressed three conferences in Moscow during December. Speaking in the Russian language, Dr. Sattler lectured on "The Importance of Pleural Biopsy for Diagnosis and Therapy of Pulmonary Diseases." The conferences at which Dr. Sattler presented his addresses were: Institute for Thoracic Surgery, Academy of Medical Sciences; Institute for Tuberculosis; Institute for Experimental Pathology and Therapy of Cancer, Academy of Medical Sciences.

ANNOUNCEMENT

A Postgraduate Course on Bronchoesophagology, under the direction of Drs. Chevalier L. Jackson and Charles M. Norris, will be presented in the Department of Laryngology and Bronchoesophagology, Temple University Medical Center, Philadelphia, November 9-20. Tuition for the course is $250. An application and further information may be obtained by writing to: Jackson-Research, Laboratory 604, Temple University Medical School, 3400 North Broad Street, Philadelphia 40, Pennsylvania.

Report of the Council on Postgraduate Medical Education

Postgraduate Courses Sponsored by the Council During the Period, 1946-1959 Registration

Chicago Courses	
1946	25
1947	62
1948	44
1949	38
1950	51
1951	51
1952	65
1953	92
1954	40
1955	59
1956	67
1957	53
1958	108
1959	Oct. 5-9
Total	755

New York City Courses	
1948	76
1949	86
1950	110
1951	138
1952	97
1953	140
1954	98
1955	114
1956	96
1957	119
1958	81
1959	Nov. 9-13
Total	1,155

Philadelphia Courses	
1948	62
1949	44
1950	47
1951	54
1952	87
1953	66
1954	80
1955	93
1956	84
1957	42
1958	58
1959	54
1960	Mar. 14-18
Total	773

Milwaukee Courses	
1951	68
1952	41
1953	59
1957	25
Total	193

California Courses		
1948	43	S. F.
1949	71	S. F.
1951	36	S. F.
1952	43	S. F.
1954	47	S. F.
1955	137	L. A.
1956	104	S. F.
1957	106	L. A.
1958	54	S. F.
1959	Dec. 7-11	L. A.
Total	641	

Newark Courses	
1951	85
1955	75
1957	44
1959	29
Total	233

Nashville Courses	
1951	50
1957	40
Total	90

New Orleans Course	
1954	58

Pittsburgh Courses	
1953	40
1955	49
Total	89

Atlanta Course	
1958	43

59 Postgraduate Courses — *Total Registration, 1946-1959.....4,030*

Postgraduate courses on diseases of the chest have been given in the following countries during the period 1951 to present date: Havana, Cuba—1951—1952—1954; Manila, Philippines—1951—1953—1955; Lima, Peru—1953.

The College has cooperated with medical schools and clinics in presenting postgraduate courses in the following cities: Cleveland, Ohio; Denver, Colorado; Houston, Texas; Los Angeles, California; Minneapolis, Minnesota; Portland, Oregon and Salt Lake City, Utah.

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